Dissertation

Evaluating the quality of lifetime medicines - results from Asia and the health consequences of falsified medicines

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ABSTRACT

By far the most challenging tasks in assuring the quality and safety of pharmaceutical products and the delivery of effective healthcare to patients are to detect adulterated, fake, unregulated, and/or poor quality medicines, also termed as "falsified medicines", and to prevent their distribution. Falsified medicines are endemic in the global drug supply chain, including traditional distribution settings, unregulated sectors, and on the internet. Additionally, substandard medicines, which are produced by legitimate manufacturers but fail to meet basic quality control tests, pose another risk to patients' health. At best, these poor quality medicines are ineffective; at worst, they result in death. These life-threatening medicines are on the rise in both therapeutic and geographic scope, threatening patients' lives, and profiting organized criminal actors involving illicit medicines. Yet, despite these clear threats, surveillance is extremely limited, with available data pointing to an increasing global health crisis worldwide that is yet to be addressed.

The aim of this study was to investigate the situation of substandard and falsified medicines and the threat they pose to public health. The quality of two lifestyle medicines – omeprazole and pioglitazone – was examined in samples collected during surveys in Cambodia and Myanmar, and in addition a study of the public health consequences of falsified medicines was carried out based on evidence collected from the literature.

In 2014, quality assessment of omeprazole samples collected from Myanmar showed high failure rates in pharmacopoeial tests, especially in dissolution tests. The results indicated a high prevalence of substandard omeprazole in the country, and possible causes were investigated by means of detailed evaluation of the in vitro dissolution profile,

scanning electron microscopy (SEM), and X-ray computed tomography (X-ray CT) imaging of the internal structure.

Further evaluation of the quality of omeprazole purchased from internet sources and personally imported into Japan showed variations in the quality of the same product from the same manufacturer distributed in developing and developed countries, by comparing personal import samples with the products previously collected during the surveys in Cambodia and Myanmar.

Quality assessment of pioglitazone collected in China, Myanmar and purchased from internet sources revealed similar quality problems, although most of the pioglitazone samples collected from Shanghai, China were satisfactory. In terms of quality, most of the unsatisfactory samples failed in the dissolution test. The results of this study result suggest that continued monitoring is necessary particularly in Myanmar, Cambodia and for personal import medicines.

To investigate the health consequences of falsified medicines for patients, a study of the literature was carried out to identify published papers dealing with this issue. Data were collected on the mortality and morbidity of the populations exposed to falsified medicines, focusing on the scale of the issue, the geographic extent, the medicines affected, and the harm caused. The study indicates that falsified medicines have impacted substantially on public health worldwide, and also suggests that developed and developing countries are almost equally affected.

The results of the present studies have enhanced our understanding of the scope of the problem of falsified and substandard medicines, and led to several important conclusions. The problem of poor and variable drug quality is identified as a major public health challenge. It can lead to the therapeutic failure, loss of lives, and loss of trust in the health

system. Moreover, online sites selling medicines for personal use pose a substantial risk to drug quality. To eliminate the problem of poor drug quality and ensure access of people to safe and effective medicines, it will be necessary for all stakeholders to work together in undertaking a comprehensive assessment of the quality of medicines accessed locally and/or internationally, and also to develop effective regulatory controls to prevent the manufacture and distribution of substandard and falsified medicines.

To My Beloved Parents & Teachers

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DECLARATION

The work presented in this report is my own. Where data and information have been derived from other sources, I confirm that this has been indicated in the thesis.

Chapter 2 of this dissertation, in part, has been published in BMC Pharmacology and Toxicology, 2017. The dissertation author is the main and corresponding author, Dr. Kazuko Kimura is the primary investigator and co-author, Dr. Hirohito Tsuboi and Dr. Naoko Yoshida are co-authors of this paper.

Chapter 3, of this dissertation, in part, has been submitted for publication in Tropical Medicine & International Health, 2017. The dissertation author is the main and corresponding author, Dr. Kazuko Kimura is the primary investigator and co-author, Dr. Hirohito Tsuboi and Dr. Naoko Yoshida are co-authors of this paper.

Chapter 5, of this dissertation, in part, has been submitted for publication in BMC Public Health, 2017. The dissertation author is the main and corresponding author, Dr. Kazuko Kimura is the primary investigator and co-author, Dr. Hirohito Tsuboi and Dr. Naoko Yoshida are co-authors of this paper.

Signature..... Date.....

THESIS PUBLICATIONS

1. **Rahman MS**, Yoshida N, Tsuboi H, Keila T, Sovannarith T, Kiet HB, Dararth E, Zin T, Tanimoto T, Kimura K. Erroneous formulation of delayed-release omeprazole capsules: alert for importing countries. BMC Pharmacol Toxicol. 2017 May 3;18(1):31. doi: 10.1186/s40360-017-0138-5.

2. **Rahman MS**, Yoshida N, Sugiura S, Tsuboi H, Keila T, Kiet HB, Zin T, Tanimoto T, Kimura K. Quality of omeprazole purchased via the internet and personally imported into Japan: Comparison with products sampled in other Asian countries. Tropical Medicine & International Health (Under Review).

3. **Rahman MS**, Ibarra AV, Yoshida N, Tsuboi H, Kimura K. Public health concerns of substandard antidiabetic medicine: Quality estimation of pioglitazone by a cross-sectional survey (Drafted Manuscript).

4. **Rahman MS**, Yoshida N, Tomizu N, Endo J, Miyu O, Tsuboi H, Kimura K. The Health Consequences of Falsified Medicines: A Study of the Published Literature. BMC Public Health (Under Review).

5. Islam MdR, Yoshida N, Kimura K, Uwatoko C, **Rahman MS**, Kumada S, Endo J, Ito K, Tanimoto T, Zin T, Tsuboi H. An investigation into the quality of medicines in Yangon, Myanmar. Journal of Pharmaceutical Policy and Practice (Under Review).

CONFERENCE PUBLICATIONS

1. **Rahman MS**, Ito K, Uwatoko C, Yoshida N, Tsuboi H, Tanimoto T, Kimura K. An investigation of the status of counterfeit and substandard medicines in Myanmar 2014-quality estimation of Omeprazole and Donepezil. 30th Japan Association for International Health Congress. Abstract published in Journal of International Health. 31(3): 219 -219. 2016.

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3. **Rahman MS**, Maeda E, Chang S, Yoshida N, Tsuboi H, Kimura K. Public health concerns of substandard antidiabetic medicine: Quality estimation of pioglitazone by a cross-sectional survey. Young Scientists Satellite Conference of the 6th Pharmaceutical Sciences World Congress 2017, Uppsala, Sweden.

4. **Rahman MS**, Maeda E, Chang S, Yoshida N, Tsuboi H, Kimura K. Public health concerns of substandard antidiabetic medicine: Quality estimation of pioglitazone by a cross-sectional survey. 6th FIP Pharmaceutical Sciences World Congress 2017, Stockholm, Sweden.

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LIST OF ACRONYMS AND ABBREVIATIONS

API- Active Pharmaceutical Ingredient

BP: British Pharmacopoeia

DDF: Department of Drugs and Food

DEG-Diethylene glycol

EU- European Union

FDA- Food and Drug Administration

FDA: Food and Drug Administration

FIP- International Pharmaceutical Federation

GERD- Gastroesophageal Reflux Disease

HPLC: High-performance liquid chromatography

JPMA: Japan Pharmaceutical Manufacturers Association

MRA- Medicine Regulatory Authority

NCD- Non-Communicable Disease

NF: National Formulary

OTC- Over the Counter Drug

PCA- Principal Component Analysis

PSI- Pharmaceutical Security Institute

SEM: Scanning electron microscopy

SSFFC- Substandard/spurious/falsely-labelled/falsified/counterfeit

UK-United Kingdom

USA-United States of America

USP: United States Pharmacopoeia

UV- Ultraviolet

WHO: World Health Organization

WHO-World Health Organization

X-Ray CT: X-Ray computed tomography

Chapter 1

Introduction to the research project

1.1. General introduction

This thesis and the research reported herein are focused on the issue of 'falsified and substandard medicines'. Specifically, the quality of delayed-release omeprazole capsules and pioglitazone tablets collected in several Asian countries was examined, and a review of the literature was carried out to investigate the actual health consequences of falsified medicines. The aims of this introductory chapter are to introduce the research topic, to state the problem that has prompted the research, and to describe the contribution to knowledge the research makes. The chapter finishes with an outline of the structure of the thesis.

1.2. Research focus, subject issues and interests

Safety of medicines is essential for patients' health. But providing safe medicines is a complex task, as the circulation of falsified or substandard medications is a global problem with a significant impact on the patients who ingest them (Hellstrom, 2011; Oshikoya & Senbanjo, 2010). There has been increasing international concern about the threat of falsified and substandard medicines (Gautam et al., 2009). The published estimates about the global prevalence of falsified medicines range from 1–50%. This problem is, however, much more severe in the developing countries; the World Health Organization estimates that about 25% of the medicines consumed in developing countries may be falsified (Newton et al., 2006; Green, 2006; WHO, 2006). In July, 2013, WHO has launched The Global Surveillance and Monitoring System for SSFFC medical products in West African region and since then almost 1400 SSFFC medical products have been reported (WHO, 2017).

Nevertheless, there are very few published data allowing estimation of the extent of the problem and the impact on public health. Only 5–15% of the 191 member states of the World Health Organization (WHO) report cases of substandard and falsified drugs. Many data have been interpreted uncritically, and some are inaccurate, so it is difficult to generalize about the epidemiology of poor quality medicines (Newton et al., 2010; Caudron et al., 2008; Newton et al., 2006; WHO, 1999a).

Non communicable diseases (NCDs) account for about 35 million deaths each year, of which 80% occur in low and middle income countries. Most of the conditions that cause these deaths can be treated with safe and effective essential medicines. Unfortunately access to good quality lifestyle and chronic disease medicines is generally poor in many of those countries. In 2009, a southwest China newspaper reported on a substandard version of the diabetes drug glibenclamide (also called glyburide) found to contain six times the pharmacopeia standard dose (Xiang, 2009). The implementation of effective approaches to combating falsified medicines is a matter of great importance for any country. However, since the last survey conducted in Myanmar in 1999 (Wondemagegnehu 1999), little research has been reported, particularly in that country (WHO, 1999b). During the past few decades, many pharmaceutical industries and distribution channels have flourished globally, which led to an increase in the number of products circulating in local and international markets. At the same time, however, the presence of falsified and substandard drugs has increased substantially as a result of ineffective regulation of the manufacture and trade in pharmaceutical products by both exporting and importing countries (Lamy & Liverani, 2015). In these circumstances, systemic study is needed in order to obtain independent information about the situation

of the medical products in the countries and the problem of falsified medicines in order to help develop prevention strategies to combat drug falsification.

1.3. Contribution of the research

Box 1: Key Messages

- **What is already known in this area of research?**
  - Medicine quality is critical to patients' health - poor quality can lead to treatment failure, adverse effects, prolonged illness, and even death.
  - Data about the quality of medicines and the impact of substandard medicines on public health is limited, particularly in Myanmar, Cambodia, and for medicines purchased via the internet.
- **What does this research add?**
  - Provides an up-to-date survey of the quality of lifestyle medicines distributed in Myanmar, Cambodia, China, and obtained from internet sources.
  - Provides insight into the prevalence of substandard and variable quality medicines circulating in several South Asian countries.
  - Provides an organized summary of published data on the public health consequences of falsified medicines.
- **Recommendations**
  - The results highlight the need for continuous ongoing surveillance to monitor the quality of medicines.
  - Collaborative, comprehensive and harmonized strategies are required for addressing variability in drug quality.
  - Local regulatory authorities should be strengthened.

The high demand for medicines coupled with limited supply, weak regulatory oversight, and limited public awareness all contribute to the trade in falsified and substandard medicines. This study provides information about the current status of this problem in several countries in Southeast Asia, highlighting potential issues concerning regulation of drug distribution and patient safety. The results throw light on how authentic manufacturers and the respective regulatory authorities appear to perceive their own roles, and how they can contribute to the overall effort to combat the problem of substandard and falsified medicines. The findings should be helpful in developing a framework to assist decision-makers at national government level in developing suitable regulatory strategies.

One of the key findings of this study is that certain pharmaceutical manufacturers appear to be exporting medicines of substandard quality to Cambodia and Myanmar, while at the same time, the same manufacturers are providing higher-quality products to developed countries. Countries with comparatively weak regulatory bodies may be unable to apply stringent criteria in setting quality requirements for products and manufacturers. Therefore, product quality is not consistently assured. Thus, there is a need for continuous and ongoing monitoring of the quality of medicines from the manufacturing process through to distribution, proper storage, and usage. While longer-term solutions are being developed, it is important to carry out periodic quality testing as an evaluation and screening tool to improve current standards. This will help individual countries to protect the national drug supply by identifying potential problems, thereby enabling them to improve regulation of manufacturers, to prevent poor quality drugs from entering the market, to detect them when they do enter the market, and to punish those who manufacture and trade them.

1.4. Structure of the thesis

The report is structured as follows-

1.4.1. Chapter 2: Erroneous formulation of delayed-release omeprazole capsules alert for importing countries – starts with an introductory part outlining the background of the research, statement of the research problem and a succinct literature review. Later part discusses the research methodology in details. Results part of this chapter primarily presents the summary of the quality test results of delayed-release omeprazole capsules collected from Yangon, Myanmar in 2014 and secondarily a detailed investigation of the failure of the omeprazole samples from Cambodia in 2010 and Myanmar in 2010. Discussion part of this chapter lays out key research findings while emphasizing the problem of these substandard medicines, their main causes and research limitations. The chapter ends with concluding remarks, including some suggestions on preventive measures to stop these poor quality medicines in Cambodia and Myanmar.

1.4.2. Chapter 3: Quality of omeprazole purchased via the internet and personally imported into Japan: Comparison with products sampled in other Asian countries- this chapter is a continuation of the previous research work, extended to evaluate the quality of omeprazole available in the internet for personal import and to compare the quality with previously collected samples from Cambodia and Myanmar. The section mainly presents evidence of the quality variation of omeprazole samples from the same manufacturers in developed and developing countries. Details of the research findings are outlined in the results and discussion section of this section, followed by the conclusion.

1.4.3. Chapter 4: Public health concerns of substandard antidiabetic medicine: Quality estimation of pioglitazone by a cross-sectional survey - discusses the prevalence

of substandard pioglitazone available via the internet, as well as from Shanghai, China and Mandalay, Myanmar. Findings of this section frame several problems that may hinder the access of diabetic patients to pioglitazone of reliable quality, including unregulated internet sites that are selling pioglitazone tablets for personal use. The section conveys a strong message that when there are unmet needs from internal sources and a weak enforcement of regulations. For example, in the case of Myanmar, poor quality medicines may enter into the country even through an authorized channel.

1.4.4. Chapter 5: The health consequences of falsified medicines: A study of the published literature - this section presents a review of the published literature data about the health effects of falsified medicines on mortality and morbidity, focusing on the scale of the issue, the geographic extent, the medicines affected, and the harm caused. Published reports are summarized in a long table, arranged according to the economic status of the countries involved, region affected, therapeutic category of the medicines, number of victims by year, number of incidents by year, and the characteristics of the falsified medicines with initial discussion of the definition of substandard and falsified medicines, their causes, and potential harmful effect on the patients.

1.4.5. Chapter 6: General Conclusions and Future Directions - the thesis finishes with this chapter outlining the general conclusions of the research, policy implications and future directions for limiting the spread of substandard and falsified medicines.

The boxes in each chapter provide a brief overview of the entire chapter highlighting the background, research focus, key findings, strengths, limitations, recommendations, and significance of the study.

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Chapter 2

Erroneous formulation of delayed-release omeprazole capsules: Alert for importing countries

2.1. Introduction

There is considerable evidence that the incidence of falsified and substandard medicines is increasing, particularly in middle and lower income countries (Almuzaini et al., 2013; Newton et al., 2010; Caudron et al., 2008). There have been many well-established instances of falsified medicines in recent years (Tabernero et al., 2015; Khurelbat et al., 2014; Yoshida et al., 2014; Khojah et al., 2013; Kuramoto et al., 2015; Wang et al., 2013; Attaran et al., 2012). In addition, substandard medicines, which are prepared by legitimate manufacturers but fail to meet pharmacopoeial requirements, also constitute an enormous public health problem (Kaur et al., 2008; Onwujekwe et al., 2009; WPRO, 2005; Fernandez et al., 2011; WHO, 1999). On-going surveillance seems essential.

The substituted benzimidazoles are a class of anti-secretory compounds that suppress gastric acid secretion by inhibition of the H+/K+-ATPase enzyme system at the secretory surface of gastric parietal cells (Riedel & Leopold, 2005; Qaisi et al., 2006). Among them, omeprazole, 5-methoxy-2-([4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl)-1H-benzimidazole, is a basic compound that acts as a proton pump inhibitor, and is used in the treatment of acid reflux and heartburn (Hardman et al., 1996). It is acid-labile, being degraded rapidly in aqueous solution at low pH (Mathew et al., 1995; Pilbrant & Cederberg, 1985). Pre-formulation studies confirmed that it is susceptible to moisture, heat and acidic solvents (Davidson & McCallum, 1996; Lindberg et al., 1987). Therefore, to avoid degradation of omeprazole by acid in the stomach, the drug must be enteric-coated (Migoha et al., 2015; Bharate et al., 2010). Consequently, omeprazole dosage forms are prepared and marketed in an enteric-coated form that allows the

omeprazole core to be specifically released and dissolved in the duodenum (pH > 5) or terminal ileum where the pH is about 6.8 to 7.5 (Thoma & Bechtold, 2000).

Despite increasing attention to the quality of medicines for communicable diseases, focus on medicines for non-communicable diseases remains inadequate. In 2010, quality test results of omeprazole in Cambodia indicated that more inspection and monitoring of medicines for non-communicable diseases is necessary (Yoshida et al., 2014). The availability of falsified and substandard medicines in Myanmar was reported by WHO in 1999 (WHO, 1999), but since then there has been no systematic survey in the country, and the current situation is unclear, except for sporadic reports of falsified medicines. Based on our experience in Cambodia during 2006-2013 (Yoshida et al., 2014), where we encountered various poor quality (mostly substandard) medicines, omeprazole was chosen as one of the target medicines for investigation in Myanmar, in consultation with the Department of Food and Drug Administration (FDA), Myanmar. Among 65 samples of omeprazole capsules collected in Myanmar in 2014, we found high failure rates in pharmacopoeial tests, especially dissolution tests. This is broadly consistent with other reports of substandard drugs in Cambodia (Khan et al., 2010; Khan et al., 2011).

The aim of the present study was to establish the cause of the high failure rate of omeprazole capsules from Cambodia and Myanmar in dissolution tests by means of detailed evaluation of the in-vitro dissolution profile, as well as scanning electron microscopy (SEM) and X-ray computed tomography (X-ray CT) examinations.

Details of the omeprazole samples collected from Cambodia in 2010 and their quality test results have been reported by Yoshida et al in BMC Pharmacology and Toxicology in 2014. This chapter will primarily focus on the omeprazole samples

collected from Myanmar. In the later part, details of the investigation of both Cambodian and Myanmar samples will be presented.

Box 2: Summary of Chapter 2

- **Research focus**
  - Quality investigation of delayed-release omeprazole capsules from Myanmar and the cause analysis of the failure of omeprazole samples from Cambodia and Myanmar.
- **Key findings**
  - Circulation of substandard omeprazole medicine in the countries is identified.
  - Poor enteric coating of the granules and the granules without enteric coating are detected.
- **Strengths and limitation of the study**
  - Provides important information to the respective regulatory authorities that omeprazole medicine was found with high failure rates, especially in the dissolution test.
  - Samples were insufficient for detailed examination to confirm the coating material used during the manufacture of the enteric coated pellets or if there was inadequate coating method.

2.2. Methods

2.2.1. Sample collection

2.2.1.1. Sampling site and area

Delayed release omeprazole capsules and tablets were purchased from pharmacies, hospitals, and wholesalers located in Yangon, Myanmar during 27 September to 4 October, 2014. Sampling sites in Yangon were government hospitals with 200-500 beds, private hospitals having pharmacies on their properties and wholesalers identified by Myanmar FDA. Community pharmacies and clinical pharmacies in clinics were visited along the streets to hospitals.

2.2.1.2. Sample size and collected amount per sample

At least 40 dosage units of each medicine were to be collected. The same sample code was assigned to each sample of the same product with the same batch number collected at the same shop at the same time. For tablets and capsules, 100 dosage units were collected in principle. Forty dosage units were kept by the Department of Food and Drug Administration (FDA), Ministry of Health, Myanmar for confirmation testing in the event of failure at Kanazawa University, and the rest were sent to Kanazawa University for authenticity investigation and analysis.

2.2.1.3. Sampling procedure

Two teams were assigned for sampling. Each team consisted of a local supervisor, a local assistant, and one or two researcher(s) from Japan. A sampling form containing observed information of the outlet and product information was completed by samplers just after the purchase of each sample (Appendix 1). Samples were sealed in a plastic bag and a serial number label was attached immediately after the collection. Vehicles were air-conditioned.

2.2.2. Observation test

For all the samples the observation inspection was made with the help of the "Tool for Visual Inspection of Medicines" produced by the International Council of Nurses in partnership with the United States Pharmacopoeia (USP) and modified by the Military and Emergency Pharmacists Section of FIP (FIP, 2014) (Appendix 2).

2.2.3. Authenticity investigation

Authenticity investigation was performed according to the modified WHO method (WHO, 1999). The procedure was to ask the manufacturers stated on the label of the product about authenticity and also to ask the Medicines Regulatory Authorities (MRA) of manufacturing countries about the legitimacy of the products and manufacturers. Questionnaires, including pictures of the sample and if requested some tablets, were sent to the manufacturer and MRA for evaluation of authenticity (Appendix 3, 4, 5, & 6). Registration numbers in Myanmar were verified by the FDA, Ministry of Health and Sports, Myanmar (Appendix 7 & 8).

2.2.1. Analytical procedure

2.2.1.1. Materials and reagents

United States Pharmacopeia (USP) reference standard omeprazole was procured from USP Convention. Authentic omeprazole standard capsules (Losec) were provided by AstraZeneca. Lansoprazole (internal standard) was from Sigma Aldrich (India). $NaH_2PO_4.2H_2O$, Na_2HPO_4, Na_3PO_4, KH_2PO_4 and other chemicals of reagent grade were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Distilled water was used for the preparation of HPLC eluents.

The investigational samples consisted of 154 samples of hard gelatin capsules containing 20 mg of omeprazole in enteric-coated pellets and two tablet samples

purchased from different drug stores in Cambodia in 2010 and Myanmar in 2014. These samples were from 53 different manufacturers in seven countries. Samples were stored below 25 ºC after collecting and all the quality analysis of the samples was finished before expiration date of the samples. After quality-testing as required by the indicated pharmacopoeia, we selected five samples for further investigation based on the gravity of their failure in the dissolution test.

2.2.2. HPLC determination of omeprazole

HPLC was run on a Phenomenex Gemini NX C18 column (150 x 4.6 mm), with a Prominence HPLC Photo Diode Array Detector (SPD-20A/20AV Series; Shimadzu, Kyoto, Japan). The temperature of the column oven was set to 25 °C. Elution buffer was prepared by dissolving 1.17 g $NaH_2PO_4.2H_2O$ and 1.06 g Na_2HPO_4 in 1000 ml of water; the pH was adjusted to 6.8. The column was eluted with a mixture of phosphate buffer and acetonitrile (60:40) at a flow rate of 0.5 ml/min. Detection wavelength and injection volume were 302 nm and 10 µL, respectively for British Pharmacopoeia (BP) samples. For USP samples, the flow rate was 1 ml/min, detection wavelength was 280 nm, and injection volume was 10 µL.

2.2.3. Omeprazole identification, quantity and content uniformity tests

Identification, Quantity and content uniformity tests of omeprazole samples were carried out according to the modified method of BP 2010 and 2015 (BP, 2010; BP, 2015) or USP 34 and 37 (USP, 2011, USP, 2014) as indicated in the package insert or on the outer package of each sample. For the identification test, a chromatogram of the sample was compared with that of reference standard omeprazole. The retention time of the principal peak in the sample chromatograms was similar to that of the peak of standard omeprazole. Standard solutions were prepared by dissolving accurately weighed

quantities of omeprazole (reference standard) and lansoprazole (internal standard) in the diluent to obtain solutions with concentrations of 0.2 mg/ml and 0.1 mg/ml, respectively. From these stock solutions, 5 diluted omeprazole solutions (0.2, 0.15, 0.1, 0.05 and 0.025 mg/ml) were prepared. The relationship between the peak area and concentration of each reference standard was linear within the range of 25-200% of the active ingredient (r^2 = 0.999-1.000), and the quality test was performed within that range.

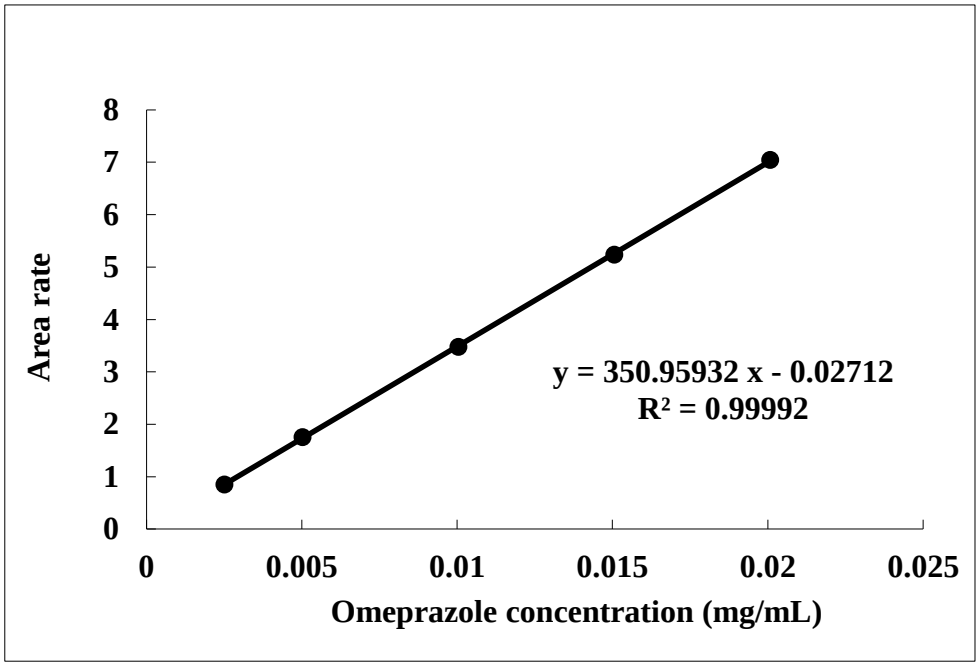

Figure 2.1: Calibration curve of omeprazole reference standard

2.2.3.1. Acceptance criteria

In the pharmacopoeial test, quantity and content uniformity acceptance criteria of the delayed release omeprazole capsules were as follows-

- **Quantity test**

✓ **BP**: Omeprazole tablets/capsules contain the equivalent of not less than 95.0% and not more than 105.0% of the labeled amounts of omeprazole.

- ✓ **USP**: Omeprazole tablets/capsules contain the equivalent of not less than 90.0% and not more than 110.0% of the labeled amounts of omeprazole.

- ➢ **Content Uniformity test**

Calculation of acceptance value (AV); calculate the acceptance value by the formula- AV= $|M-\bar{x}| + KS$ where, M: reference value; $\bar{x}$: mean of individual contents; K: acceptability constant, K=2.4 when the number of unit is 10, and the K=2 when the number of unit is 30; S: standard deviation of the sample. 10 units were assayed individually, the requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units was less than or equal to 15 for the first stage. In 2nd stage AV of 30 units ≤ 15 (1st stage 10+2nd stage 20 more units). No individual content of any dosage unit is less than 0.75M % or more than 1.25M% (M=Reference value).

2.2.4. Omeprazole dissolution test and examination of dissolution profile

Dissolution test was performed according to the BP or USP as indicated by the sample products. BP Samples were exposed to 700 ml phosphate buffer, pH 4.5, for 45 minutes in acid stage and 900 ml phosphate buffer, pH 6.8 for 45 minutes in buffer stage (BP, 2010; BP, 2015). USP samples were exposed to 500 ml of 0.1 N HCl for 2 hours in acid stage and 900 ml of phosphate buffer, pH 6.8 for 30 minutes in buffer stage (USP, 2011, USP, 2014). The dissolution test was conducted with a NTR-VS 6P dissolution apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan). Drug release studies were carried out by paddle method. The paddle was set to rotate at 100 rpm and the temperature was maintained at 37 ± 0.5 °C.

To examine the dissolution profile, 3 capsules were used. Since all the failed samples were BP samples, in the investigation with the acid stage, test samples were exposed to 700 ml phosphate buffer, pH 4.5, for 45 minutes. After 45 minutes, a 5 ml aliquot was

withdrawn from each vessel for quantification by HPLC. Then 200 ml of phosphate buffer, pH 7.6, was added to adjust the final pH to 6.8 (buffer stage). In this stage, 5 ml aliquots were withdrawn from each dissolution vessel at 5, 15, 30, 45, and 60 minutes for quantification by HPLC. In the investigation without the acid stage, samples were exposed to the buffer stage directly without the previous acid stage, and samples were collected in the same manner as described above.

2.2.4.1. Acceptance criteria

In the pharmacopoeial test, quantity and content uniformity acceptance criteria of the delayed release omeprazole capsules were as follows-

- **Dissolution test**

✓ **BP**

Acid Stage (45 minutes)- Stage 1: Each unit of 6 capsules is not more than 10%; Stage 2: Average value of 12 units not more than 10% and no unit is greater than 25%; Stage 3: Average value of 24 units not more than 10% and no unit is greater than 25%

Buffer stage (45 minute)- Stage 1: no unit is less than Q+5% (Q=65); Stage 2: Average value of 12 units is more than or equal to Q (Q=65) and no unit is less than Q-15%; Stage 3: Average value of 24 units more than or equal to Q (Q=65), not more than 2 units is less than Q-15% and no unit is less than Q-25%

✓ **USP**

Acid Stage (120 minutes)- Stage 1: Each unit of 6 capsules is not more than 15%; Stage 2: Average value of 12 units not more than 20% and no unit is greater than 35%; Stage 3: Average value of 24 units not more than 20% and no unit is greater than 45%

Buffer stage (30 minutes)- Stage 1: no unit is less than Q+5% (Q=75); Stage 2: Average value of 12 units is more than or equal to Q (Q=75) and no unit is less than Q-

15%; Stage 3: Average value of 24 units more than or equal to Q (Q=75), not more than 2 units is less than Q-15% and no unit is less than Q-25%.

2.2.5. Scanning electron microscopy

Surface morphology of omeprazole granules was characterized by means of scanning electron microscopy on a Hitachi S-3400 instrument equipped with a Hitachi E-1010 ion sputter device. A few omeprazole granules were removed from the capsule shell, mounted on a stub of metal with adhesive, coated with platinum, and observed.

2.2.6. X-Ray computed tomography

X-Ray CT of the samples was conducted using an inspeXio SMX-100CT (Shimadzu) equipped with a sealed tube type micro focus X-ray generator with a maximum output of 100 kV, and a high-sensitivity image intensifier. The sample granules were positioned between the X-ray generator and the X-ray detector, and X-ray fluoroscopic data was collected from every angle by rotating the sample through 360^{o}. Finally, computed tomographic images (CT images) were calculated from the obtained data.

2.2.7. Statistical analysis

Statistical analyses were performed using Microsoft Excel and SPSS 19.0.0 (IBM SPSS Inc. Chicago, IL, USA). Statistical differences between the experimental groups were analyzed by Student's t test. Statistical significance was evaluated at the 5% level.

2.3. Results

In Myanmar, 2014, a total of 65 omeprazole samples from 21 different manufacturers of four different countries were collected. Details of the samples are outlines in Table 2.1.

Table 2.1: Outline of the omeprazole samples collected from Yangon, Myanmar in 2014

Country	Shop category	No. of samples	Country of manufacturer	
		n (%)	Domestic n (%)	Imported n (%)
Myanmar, 2014 (n = 65)	**Pharmacy**	35 (53.8)	0 (0)	65 (100)
	Hospital	26 (40)		
	Wholesaler	4 (6.2)		

2.3.1. Observation result

2.3.1.1 Pharmaceutical shops

All shops were equipped with awnings to protect medicines from direct sunlight. The average temperature in shops without air-conditioning was 30.8±2.2 0C while 28.6±2.6 0C with air-conditioning (t-test, $p<0.01$). An average humidity in shops without air-conditioning was 69.3±8.7 % while 67.90±12.4 % (t-test, n.s.). At some shops, a motorbike, a dog, a cat or a person eating was observed in the dispensing area.

2.3.1.2. Sample observation

As per the result, two of the sample did not contain any box. Each Strip was found without any type of packaging. Most of the container did not contain tamper proof sealing. Manufacturer name was not found in case of two samples. Among 65 sample collected, 14 samples did not have either any logo or hologram. Product insert was not found in 9 samples. Mixed colored granules were also observed in a sample the result of which will be discussed separately in the later part.

2.3.2. Authenticity investigation

2.3.2.1. Verification of origin/source of the products

According to the questionnaire sent to the manufacturers, 2 manufacturers have replied by 20 May 2015. Two samples out of 65 (3.4%) were confirmed as genuine products and no falsified medicines was reported (Table 2.2). Most manufacturers had a contact e-mail address, but in many cases, there was no reply even after a reminder e-mail.

2.3.2.1. Legitimacy of the manufacturers and products

Questionnaires were sent to 5 MRAs in manufacturing countries (Bangladesh, India, Myanmar, Singapore, and Thailand) by e-mail in December 2014. Unfortunately, no response was obtained from the any of the MRAs except from Myanmar. All manufacturers and samples of omeprazole (100 %) were found to be registered to Myanmar FDA (Table 2.2).

Table 2.2: Authenticity, legitimacy, and registration verification result of omeprazole

Category		Replies (total number)	Reply on samples (number of samples)	Authentic		
				Yes	No	Unknown
Authenticity of the product	**Manufacturer**	2 (21)	4 (65)	2		2
Legitimacy of the manufacturer	**Manufacturing country**	0 (4)	0 (65)			
Registration of the manufacturer			21 (21)			
Registration of the product			65 (65)			

Table 2.3: Quality test result of omeprazole from Cambodia in 2010 and Myanmar in 2014

Country	Quality tests	Pass n (%)	Fail n (%)	Pending[1] n (%)
Cambodia, 2010 (Yoshida et al, 2010)	**Quantity**	54 (59.3)	22 (24.2)	15 (16.5)
	Content Uniformity	31 (34.1)	14 (15.4)	46 (50.5)
	Dissolution	42 (46.2)	45 (49.4)	4 (4.4)
Myanmar, 2014	**Quantity**	42 (64.6)	23 (35.4)	0 (0)
	Content Uniformity	56 (86.2)	9 (13.8)	0 (0)
	Dissolution	48 (73.8)	17 (26.2)	0 (0)

[1] Insufficient material was available for full testing

Among the 156 omeprazole samples collected, 45 (28.8%) were unacceptable in the quantity test, while 23 (14.7%) were unacceptable in the content uniformity test. In the dissolution test, 90 samples (57.7%) were acceptable and 62 (39.7%) were unacceptable Summary of the quality test results is shown in Table 2.3 and the details are presented in Appendix 9-13.

2.3.2. Dissolution profile: Effect of the acid stage on drug release

Fig 2.2(A) shows the percent of omeprazole released in buffer from a standard sample (Losec) with and without the acid stage; in this case, the enteric coating of the granules retained its integrity in the acid stage, as expected, and the percent release of omeprazole without the acid stage was not much different from the percent release of omeprazole with the acid stage. Fig 2.2(B), 2.2(C), & 2.2(D) show the percent of drug released from the omeprazole granules of one Cambodian sample and two Myanmar samples respectively. In these cases, the pattern of drug release in buffer without the acid stage was significantly higher than that with the acid stage, suggesting that the enteric coating of the failed samples was not fully effective.

2.3.3. Acid degradation of omeprazole

Typical chromatograms of reference standard omeprazole, standard omeprazole sample, a passed omeprazole sample and a failed omeprazole sample are shown in Fig 2.3. The failed sample showed peaks indicating that degradation had occurred. To confirm this, reference standard (pure) omeprazole was exposed to acid (pH 4.5) and aliquots were withdrawn for HPLC analysis at 0, 10, 30, and 45 minutes.

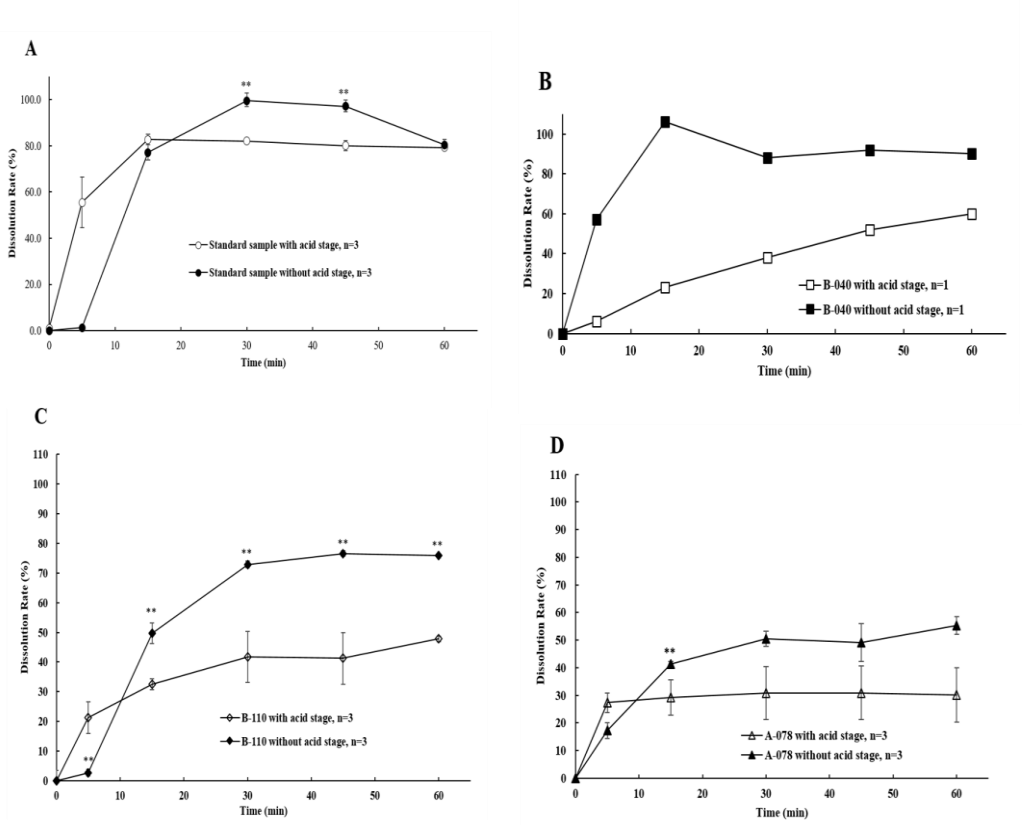

Figure 2.2: Dissolution profiles (percent release) of omeprazole in buffer stage with and without acid stage. A) The standard sample; B) failed B-040 omeprazole sample from Cambodia; C) failed B-110 omeprazole sample from Myanmar; and D) failed A-078 omeprazole sample from Myanmar. Each value represents mean ± SD of three capsules except for (B) where n = 1. Significant differences were evaluated (**$p < 0.01$) comparing percent dissolution of the capsules in with and without acid stage at each time point using student's t-test. For the dissolution profile of Cambodian sample only one capsule was used in each stage, the result of which was not available for statistical comparison

As shown in Fig 2.4, peaks of degradation products increased time-dependently, and the time course of remaining omeprazole is shown in Fig 2.5. These results are consistent with the conclusion that the failed omeprazole samples lacked effective enteric coating.

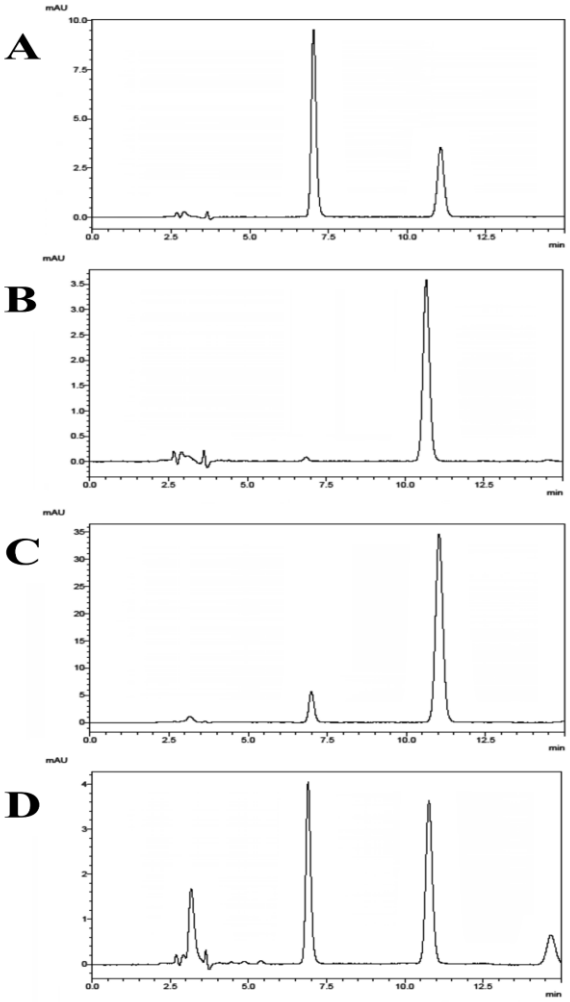

Figure 2.3: HPLC chromatogram of omeprazole samples in acid resistance stage. A) Omeprazole reference standard; B) standard omeprazole sample; C) passed omeprazole sample; and D) failed omeprazole sample

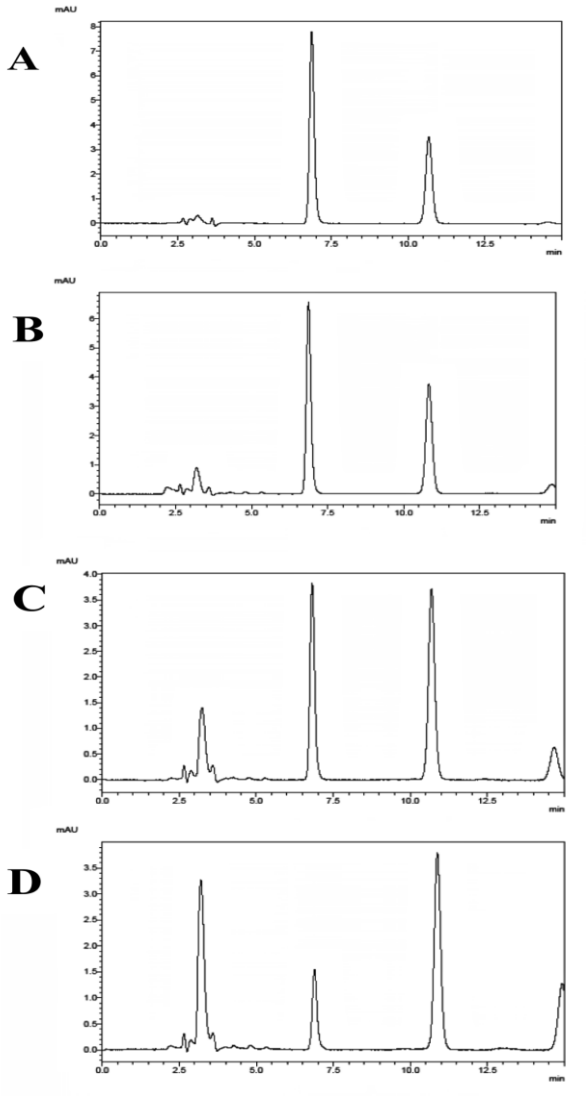

Figure 2.4: Chromatograms of pure omeprazole in acid at different time points. A) 0 min; B) 15 min; C) 30 min; and D) 45 min

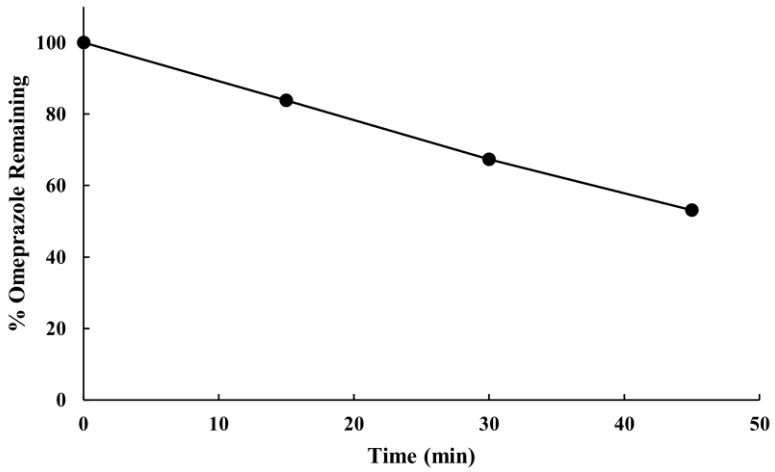

Figure 2.5: Time course of degradation of pure omeprazole in acid

2.3.4. Variability of granules in samples

Considerable variability related to the formulation or manufacturing process of omeprazole has been suggested in Cambodian samples (Yoshida et al., 2014), and we found similar variation in some Myanmar samples. The shape of the granules ranged from spherical to irregular, and different-colored granules were seen, as illustrated in Fig 2.6.

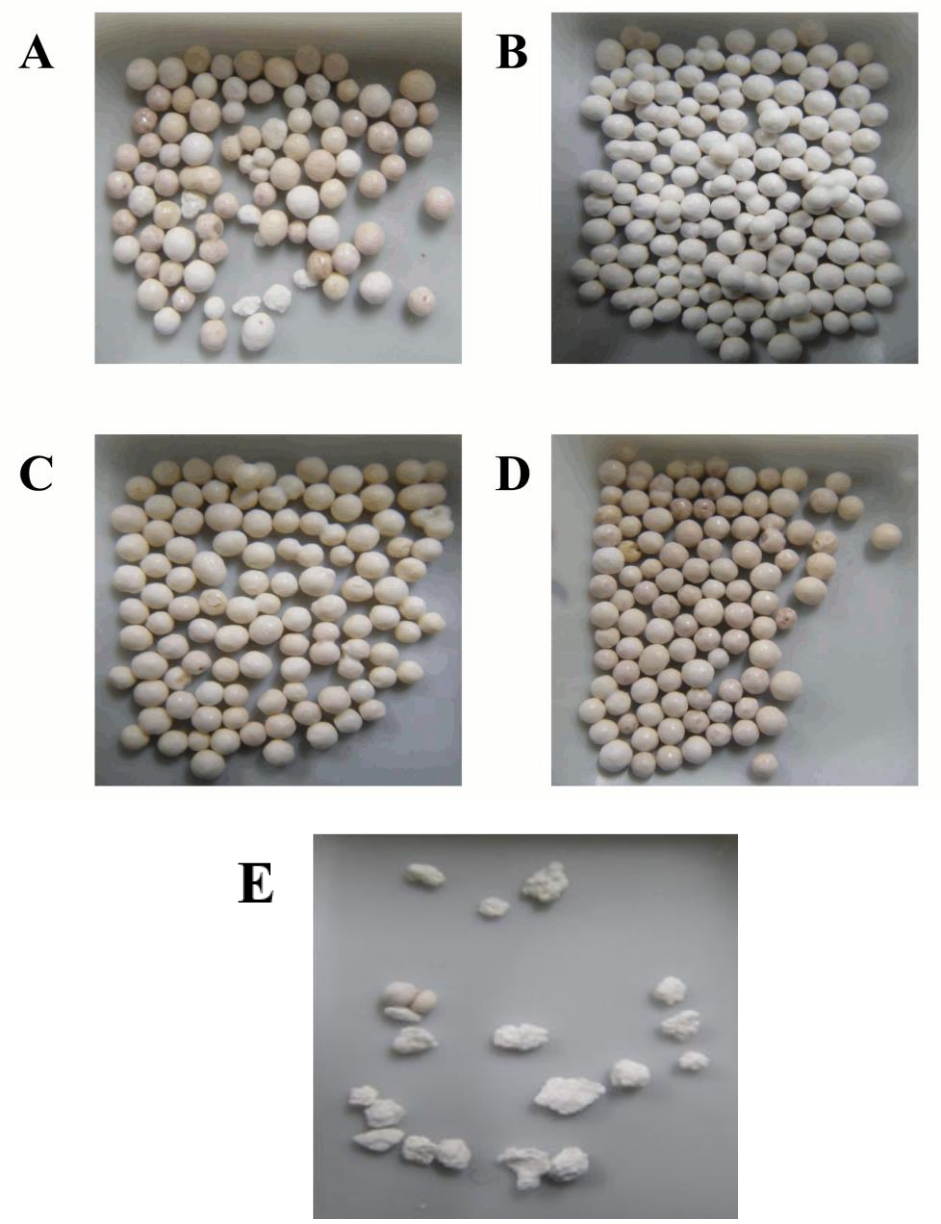

Figure 2.6: Difference in the color of granules in a capsule (sample A-078). A) Mixed granules found after opening the capsule shells; B) separated white granules; C) grey granules; D) yellow granules; and E) particles found in the capsule which were not granules

In the same capsule, there were some particles which could not be detected as granules. We isolated white, yellow, and grey granules, and quantified them individually. Irregular particles were not quantified as the amount of the particles was not enough for quantity test. The omeprazole contents in the white, grey and yellow granules were 64.1 ± 0.2, 61.4 ± 0.5 and 42.7 ± 1.7 mg (mean ± SD) per 267.8 mg of granules (average weight of six granules). The amount of omeprazole content in each 3 different granules is shown in the Table 2.4.

Table 2.4: Different amount of omeprazole content in the different colored granules in the sample A-078. Same weight (average weight of 6 capsule) was taken for all three colored granules

Granule type	White granules	Grey granules	Yellow granules
Weight	267.8 mg	267.8 mg	267.8 mg
QTY±SD	64.1±0.2	61.4 ± 0.5	42.7±1.7

2.3.5. Examination of granules by scanning electron microscopy

Representative SEM images are shown in Fig 2.7. Compared with the standard sample (A), granules from failed omeprazole samples collected in Cambodia in 2010 showed cracks in the enteric coating, along with the broken pellets. These were mixed with the regular granules in the capsule.

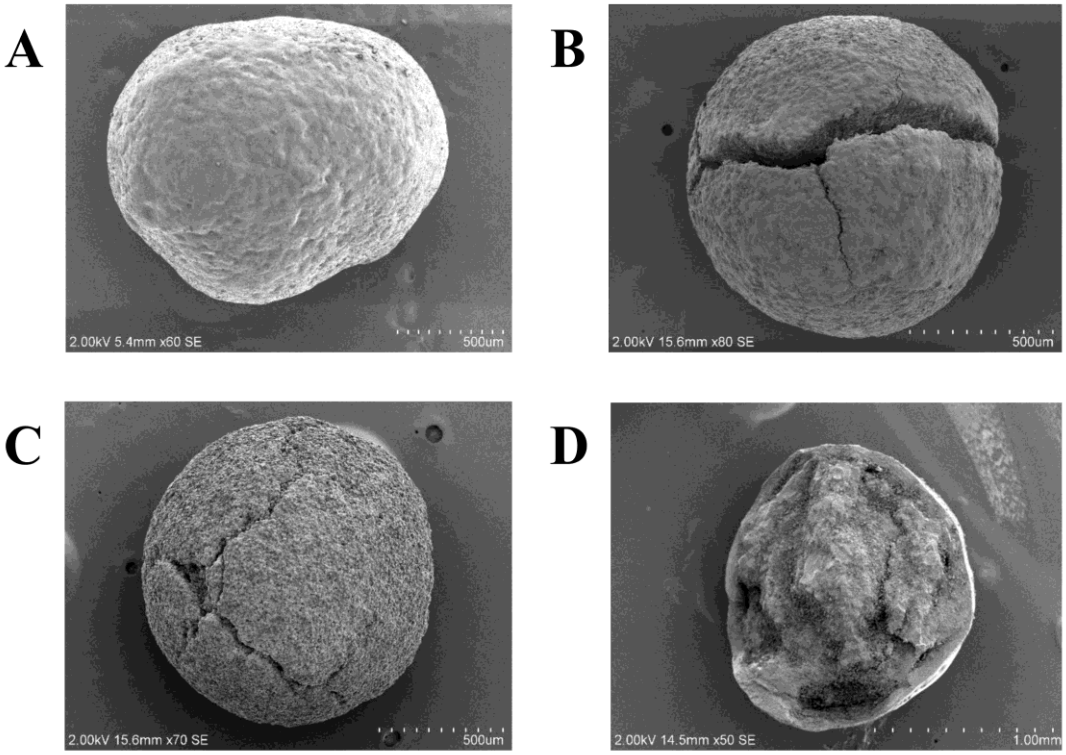

Figure 2.7: SEM images of cracked and fractured pellets found in two representative Cambodian samples. A) Standard sample; B) and C) two different granules of sample A-063; and D) Sample A-108

2.3.6. Examination of granules by X-ray computed tomography

To confirm the absence of functional enteric coating, we performed X-ray CT on selected samples that failed severely in the dissolution test and conducted a comparative study of the standard sample and failed samples. Fig 2.8 shows two different granules taken from the same capsule in a sample collected in Cambodia in 2010. One granule shows an apparently intact coating (Fig 2.8A), while the other (Fig 2.8B) has essentially no coating at all. Similar results were seen in failed samples from Myanmar, which

contained non-uniform granules, incomplete granules and granules with holes. Fig 2.9 shows representative X-ray CT images of granules from a failed Myanmar sample.

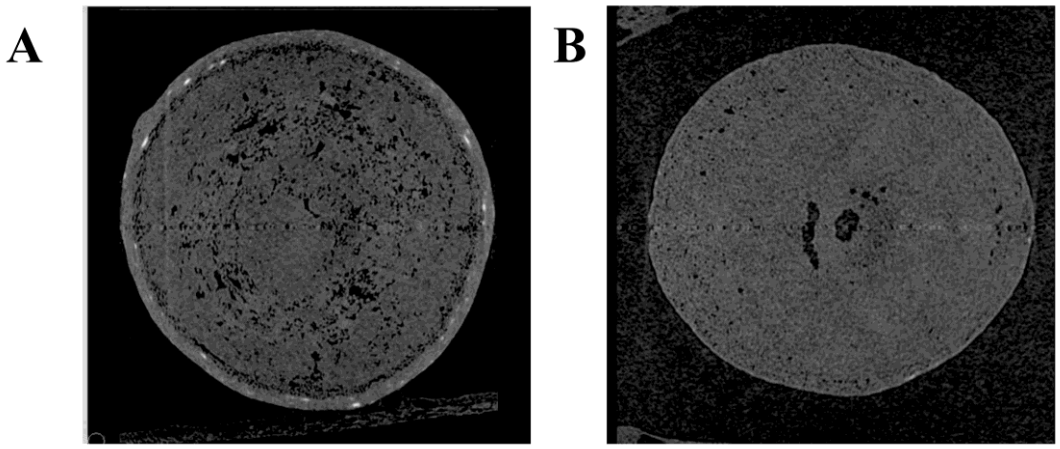

Figure 2.8: X-Ray CT images of granules found in sample B-040 collected in Cambodia in 2010. Note the presence of an apparently intact enteric-coated layer in (A) and the absence of an enteric-coated layer in (B)

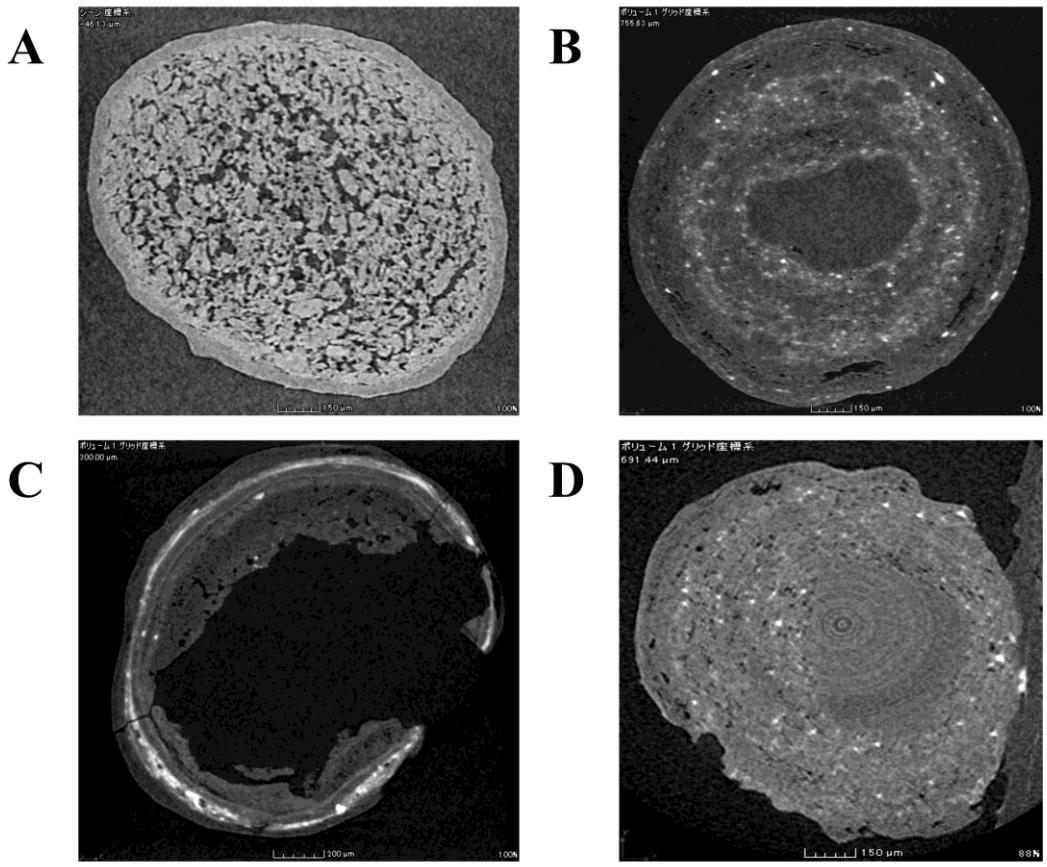

Figure 2.9: X-Ray CT images of granules found in sample A-078 collected in Myanmar in 2014. A) Standard sample; B) regular granule with apparently intact coating (white granule 1); C) irregular granule with hole (white granule 2); and D) yellow granule with incomplete coating

2.4. Discussion

Our findings for samples collected in Myanmar in 2014 indicate that the incidence and condition of substandard omeprazole medicines in Myanmar are quite similar to those in Cambodia. Yoshida et al. found that 45 out of 91 omeprazole samples collected in

Cambodia in 2010 (49.5%) were failed in the dissolution test (Table 2.3) (Yoshida et al., 2014). Among the Myanmar samples, 23 (35.4%) failed the quantity test, although the extent of failure was generally marginal. A few failed due to over-content. Moreover, significant differences were observed in the quality test, where some brands passed in most cases, while others were consistently substandard. It was particularly noteworthy that the products of certain manufacturers failed consistently.

In the present work, our prime concern was the failures in dissolution tests. Among the 17 (26.2%) failed samples from Myanmar, all failed in the buffer stage and 11 failed in both the acid and buffer stages. A key issue appeared to be that the coating of the granules did not provide good control of the drug release, so that rapid disintegration and dissolution occurred in the acid stage of the test, resulting in exposure of omeprazole to acid degradation (Qaisi et al., 2006; Mathew et al., 1995; Davidson & McCallum., 1996; Jee et al., 1992). Indeed, an HPLC analysis showed that degradation of omeprazole in the granules of failed samples during the acid stage was similar to that of pure omeprazole (Fig 2.3 & 2.4), confirming that the enteric coating was ineffective.

This conclusion was further supported by SEM images (Fig 2.7), which revealed fractured pellets and pellets with incomplete coating, together with pellets with apparently intact coating. Macroscopically, a sample from Cambodia contained two different types of granules in a single capsule, and the X-ray CT images showed that one type of granule lacked enteric coating (Fig 2.8B). Similar results were found in a sample from Myanmar, which appeared to contain three different types of granules (Fig 2.6). The X-ray CT images revealed that the coating of some granules was incomplete and some granules contained holes (Fig 2.9). Thus, there was marked inconsistency among omeprazole granules in capsules, and this suggests that at least some

manufacturers were using inadequate enteric coating technology or conditions. However, we were unable to confirm this with the manufacturers. Substandard medicines are a serious public health issue. In the case of omeprazole, substandard samples without enteric coating or with incomplete enteric coating will degrade rapidly in the acidic environment of the stomach after oral administration, and this may result in treatment failure.

It should be noted that in some cases the size of our samples was insufficient for detailed examination, and this represents a weakness of our study, in that we could not fully assess the actual extent of quality failure in our analysis. Another limitation is that; we could not confirm the coating material used during the manufacture of the enteric coated pellets or if there was inadequate coating method (e.g. inadequate equipment or inadequate coating parameters) as the response to the questionnaire from the manufacturers was minimum. Therefore, further investigation is needed to establish precisely the scale of the problem of substandard medicines in Myanmar and Cambodia. In addition, action, including regulatory measures, should be initiated to prevent the manufacture and sale of substandard medicines.

2.5. Conclusions

Samples of omeprazole capsules collected in Cambodia in 2010 and Myanmar in 2014 showed high failure rates in pharmacopoeial testing, especially in the dissolution test. In-vitro dissolution profiling, scanning electron microscopy and X-ray computed tomography showed that failed samples contained granules with ineffective (cracked or incomplete) or absent enteric coating. This would result in premature dissolution in acidic

conditions after oral administration, and could result in treatment failure. This situation is a potentially serious public health issue that needs to be addressed by regulatory authorities in Cambodia and Myanmar, possibly through legal measures and collaborative initiatives with manufacturers.

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Chapter 3

Quality of omeprazole purchased via the internet and personally imported into Japan: Comparison with products sampled in other Asian countries

3.1. Introduction

One of the major challenges to global health is the growing burden of non-communicable diseases (NCDs), which are predicted by the World Health Organization (WHO) to be the leading cause of death and disabilities worldwide by 2030 (Bollyky, 2013; WHO, 2010; WHO, 2014; WHO, 2005). Indeed, the prevalence of NCDs is estimated to be up to 27.8% in North America and 25.9% in Europe. Among the NCDs, gastroesophageal reflux disease (GERD) is one of the most common (El-Serag et al., 2014; Tack et al., 2012; Remais et al., 2012). It is often treated with a proton pump inhibitor, such as omeprazole, which is available as an over-the-counter (OTC) drug in many countries, but is a prescription drug in Japan. However, the recent rise in e-commerce and the proliferation of illicit online pharmacies has enabled patients in Japan to obtain many drugs directly, with or without a prescription (Venhuis et al., 2014; Mackey & Nayyar., 2016; Fittler et al., 2013; Nielsen & Barratt., 2009). Indeed, LegitScript's annual report in 2016 estimated that about 3,000 websites, or 10% of the world's rogue internet pharmacies, take Japan as their primary target, making it the second-largest market for illegal online drug sellers (Mackey & Nayyar., 2016; Fittler et al., 2013; LegitScript, 2016; Siva, 2009; Monteith et al., 2016). This is an important issue because of the potential for proliferation of substandard and falsified medicines.

Substandard medicines may be prepared by legitimate manufacturers, who fail to meet pharmacopoeial standards due to accidental breaches of good manufacturing practice, or may be a consequence of inadequate storage conditions in the distribution chain (Onwujekwe et al., 2009; WPRO, 2005; Fernandez et al., 2011). On the other hand, falsified medicines are produced and sold with deliberate misrepresentation of their origin, authenticity or effectiveness. These products circulate because of the constant demand for

medicines and weaknesses in national regulatory systems (Buckley & Gostin, 2013). The term falsified medicine is often broadly used to cover substandard, spurious, falsely labeled, falsified and counterfeit (SSFFC) medicinal products.

According to PSI (Pharmaceutical Security Institute) data, the prevalence of falsified medicines has increased drastically between 2002 and 2012 (Attaran et al., 2012; PSI, 2015). Even so, the reported prevalence would likely have been higher if resource-poor countries had adequate follow-up and reporting systems (Attaran et al., 2012). Also, drug-regulatory authorities in countries with adequate law enforcement and pharmaceutical companies conducting oversight do not necessarily release their records publicly (Buckley & Gostin, 2013; Attaran et al., 2012; WHO, 1999; WHO, 2017). The seriousness of the situation is illustrated by the fact that in 2010, about 67% of omeprazole samples collected from Cambodia proved to be failed in quality tests (about 98 % of these samples had been imported from various countries) (Yoshida et al., 2010). Also, about 50% of omeprazole samples from Myanmar proved to be failed in quality tests in 2014 (100% of them were imported) (Rahman et al., 2017).

In this context, the present investigation was undertaken with the primary objective of evaluating the quality of omeprazole ordered via the internet and personally imported into Japan. We also examined whether there was a quality difference between these personally imported products and products previously collected in other Asian countries and labeled as being manufactured by the same companies.

Box 3: Summary of Chapter 3

- **Research focus**
- Evaluation of the quality of omeprazole purchased via the internet and personally imported into Japan.
- Comparing the quality of these samples with that of the same products from the same manufacturers previously collected in surveys in two other Asian countries.
- **Key findings**
  - Omeprazole formulations are readily available online with or without a prescription.
  - Quality of personally imported omeprazole from online sources was satisfactory.
  - Omeprazole from the same manufacturers in developing and developed countries had variable quality.
- **Strengths and limitation of the study**
  - Present the research-based evidence of the quality variation of omeprazole samples by the same manufacturers for developed and developing countries, highlighting the need for better cooperation from manufacturers and regulatory authorities.
  - Relatively small number of the samples and sampling sites

3.2. Methods

3.2.1. Source selection and collection of samples

The Google Japan search engine was used to search for pharmacies offering omeprazole product was included in this study. The searches were performed during the

19th August to 12th September 2013. The search terms used were ‘オメプラゾール and 個人輸入’ for Japanese sites and ‘Omeprazole and personal import’ for English sites. Among the hits, pharmacies offering omeprazole 20 mg tablets or capsules were selected. Samples were purchased from them online and personally imported into Japan during August to September 2013.

3.2.2. Observation test

Each sample was assigned a code upon receipt. Details of the packaging condition, label information, product name, dosage form, dosage strength, manufacturers’ name and address, batch number, manufacturing and expiry dates, etc., were noted and evaluated according to the FIP (International Pharmaceutical Federation) checklist (Appendix 2) (FIP, 2017).

3.2.3. Authenticity investigation

The methodology of the authenticity investigation and registration verification was adopted from WHO (Yoshida et al., 2015; Khan et al., 2012; WHO, 2010). A questionnaire accompanied by a photograph of the sample was sent the relevant manufacturing company for confirmation of authenticity (Appendix 3 & 4)**.** Printed information from the product package was also verified from the manufacturers’ website. The regulatory authorities in the countries of origin and distribution were also contacted to verify the legitimacy of the products and their approval for marketing (Appendix 4 & 5).

3.2.4. Quality analysis

3.2.4.1. Materials

Reference standard omeprazole was procured from USP Pharmacopeial Convention and omeprazole standard capsules were a gift from AstraZeneca. Lansoprazole as an internal standard was purchased from Sigma-Aldrich (India). $NaH_2PO_4.2H_2O$, Na_2HPO_4, Na_3PO_4, KH_2PO_4 and other chemicals of reagent grade were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Distilled water was used for the preparation of HPLC eluents.

3.2.4.2. Analytical procedure

Quality analysis (identification, quantity, content uniformity, and dissolution test) was done according to the pharmacopoeia indicated in the package insert or on the outer package of each sample (BP, 2010; BP, 2015; USP, 2011; USP, 2014; JP, 2012; IP, 2014). A high-performance liquid chromatograph (SPD-20A/20AV Series; Shimadzu, Kyoto, Japan) with a photo diode array detector was used.

The dissolution test was performed with an NTR-VS 6P dissolution apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan). Drug release studies were carried out by the paddle method. The paddle was set to rotate at 100 rpm and the temperature was maintained at 37 ±0.5 ºC.

Standard solutions were prepared by dissolving accurately weighed quantities of omeprazole (reference standard) and lansoprazole (internal standard) in the diluent to obtain solutions with concentrations of 0.2 mg/mL and 0.1 mg/mL, respectively. From these stock solutions, 5 diluted omeprazole solutions (0.2, 0.15, 0.1, 0.05 and 0.025 mg/ml) were prepared. The relationship between the peak area and concentration was linear within the range of 25–200% of the active ingredient (r^2 = 0.999–1.000), and the

quality test was performed within that range. Acceptance criteria of the sample were set according to the respective pharmacopoeia requirements.

3.2.5. Raman spectroscopic analysis

Raman spectroscopic analysis was done using Inspector 500 (SciAps Inc., USA) equipped with higher-wavelength Raman excitation, consisting of a 300 mW 1030 nm Class III B laser and a cooled Type III-IV semiconductor detector array (spectral range 100-2500 cm-1). The concordance rate was calculated by using the NuSpec Pro software (SciAps Inc., USA). Granules of each sample were placed in front of the laser source (3 times each for 3 different granules) and the Raman spectral data were recorded and compared with those of the standard sample.

3.2.6. Data analysis

Data analysis was performed using Microsoft Excel 2010 and Principal component analysis (PCA) of Raman spectra was analyzed using the Unscrambler (Camo Software, Oslo, Norway). PCA was performed on smoothed spectra to determine potential grouping for subsequent classification.

3.3. Results

3.3.1. Online sites

A total of 31 sites selling omeprazole were found. Among them, 13 sites were in Japanese and the other 18 sites were in English. Among the 13 Japanese-language sites, none asked for a prescription, and 26 samples of 16 different products were purchased from these sites. Among the 18 English sites, 16 asked for a prescription and the other two sold omeprazole as an OTC product. Two additional samples of the same product

were purchased from these two sites. Among the 31 sites, two did not give any physical address, two sites had no contact phone number, and 6 sites did not recommend consultation with a physician or pharmacist.

3.3.2. Sample observation

A total of 28 samples were purchased, which were labeled as being from 17 different manufacturers in 6 countries, and were distributed from 7 different countries. Examination according to the FIP checklist revealed that one sample had no manufacturer's name or batch number. One sample was different from the ordered sample advertised on the site. One sample was found with loose granules outside the capsule shell, and one sample was found with a cracked capsule shell (Fig 3.1A and B).

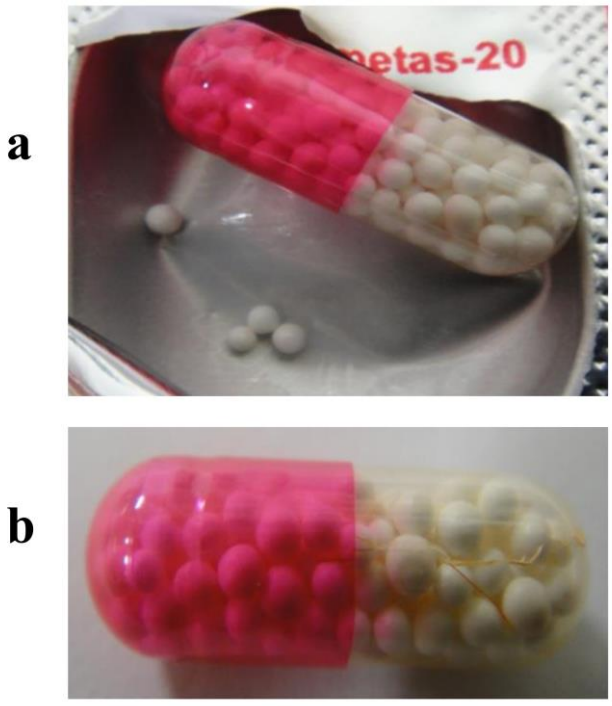

Figure 3.1: Loose granules outside the capsule shell (a) and defective capsule shell of sample (b)

3.3.3. Authenticity investigation

A questionnaire was sent to each manufacturer for product authenticity and legality investigation, as well as to the manufacturing country and country of distribution. Among the 17 manufacturers, no response was received from any manufacturer. In legality investigation, 2 manufacturing countries among 6 replied that 8 samples were legal. Among the 7 distribution countries (11 distributors), replies were received from 3 countries, and 1 distributor was found to be licensed.

3.3.4. Quality test result

Among the total of 28 samples collected, six were tablets and 22 were capsules. For the identification test, the chromatogram of a sample was compared with that of the reference standard omeprazole. The retention time of the principal peak in all the sample chromatograms was similar to that of the peak of standard omeprazole, and the UV spectra of the standard and samples were identical. The results of the quality tests are summarized in Table 3.1.

Table 3.1: Quality test results of omeprazole personally imported into Japan

Test, n=28	Quantity		Content Uniformity		Dissolution	
Judge	**Pass n (%)**	**Fail n (%)**	**Pass n (%)**	**Fail n (%)**	**Pass n (%)**	**Fail n (%)**
No. of samples (%)	26 (92.9)	2 (7.1)	26 (92.9)	1 (3.6)[2]	28 (100)	0

[2] 2nd stage test was not done for one sample because the number of tablets was insufficient.

3.3.5. Quality difference among products from the same manufacturers in different market segments

In Cambodia 2010, a study conducted by Yoshida et al. (Yoshida et al., 2014) found serious quality deficiencies, especially in the dissolution test, in omeprazole samples from some manufacturers. Similar results were reported from Myanmar in 2014 by Rahman et al. (Rahman et al., 2017). The samples from Cambodia and Myanmar had mainly failed the dissolution test in the acid stage, indicating ineffective enteric coating to protect omeprazole in the core.

Table 3.2: Quality test results of omeprazole samples of manufacturer X & Y

Test	Total samples (n)	Quantity		Content Uniformity		Dissolution	
Judge		Pass (%)	Fail (%)	Pass (%)	Fail (%)	Pass (%)	Fail (%)
Manufacturer X[3]							
Personal import	1	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Cambodia 2010	4	1 (25)	3 (75)	1 (25)	3 (75)	4 (100)	0 (0)
Myanmar 2014	18	14 (77.8)	4 (22.2)	18 (100)	0 (0)	10 (55.6)	8 (44.4)
Manufacturer Y[4]							
Personal import	3	3 (100)	0 (0)	3 (100)	0 (0)	3 (100)	0 (0)
Cambodia 2010	5	4 (80)	1 (20)	3 (60)	2 (40)	0 (0)	5 (100)
Myanmar 2014	4	3 (75)	1 (25)	4 (100)	0 (0)	0 (0)	4 (100)

[3] Pass and fail percentage of samples were calculated from the total number of samples from each sampling site.

[4] Pass and fail percentage of samples were calculated from the total number of samples from each sampling site.

Interestingly, manufacturers of those poor quality products had also produced some of the samples obtained in our current study, which successfully passed quality tests. Quality test results of omeprazole samples from two of those manufacturers (X & Y) collected previously from Cambodia and Myanmar are presented in Table 3.2 along with the results of personal import samples.

3.3.6. Raman spectroscopic analysis

Raman spectroscopy was applied to compare the products from the same manufacturers, collected at different sites. In the case of manufacturer X, the similarity of the Cambodian product to the personal import product was 68%, and that of the Myanmar product to the personal import was 62%; in contrast, the similarity of the Cambodian and Myanmar products was 94% (Fig 3.2a, b, & c). In the case of manufacturer Y, the similarity of the Cambodian product to the personal import product was 92%, and that of the Myanmar product to the personal import was 94%, whereas the similarity of the Cambodian and Myanmar products was 98% (Fig 3.3a, b, & c). For comparison, Raman spectra of the respective samples from manufacturer X & Y was further evaluated by PCA. The PCA results obtained with Raman spectra demonstrated the similar variation to clearly distinguish the samples from the same manufacturers. PCA results for the derivative Raman spectra are presented in Fig 3.4 and 3.5 for manufacturer X and Y, respectively.

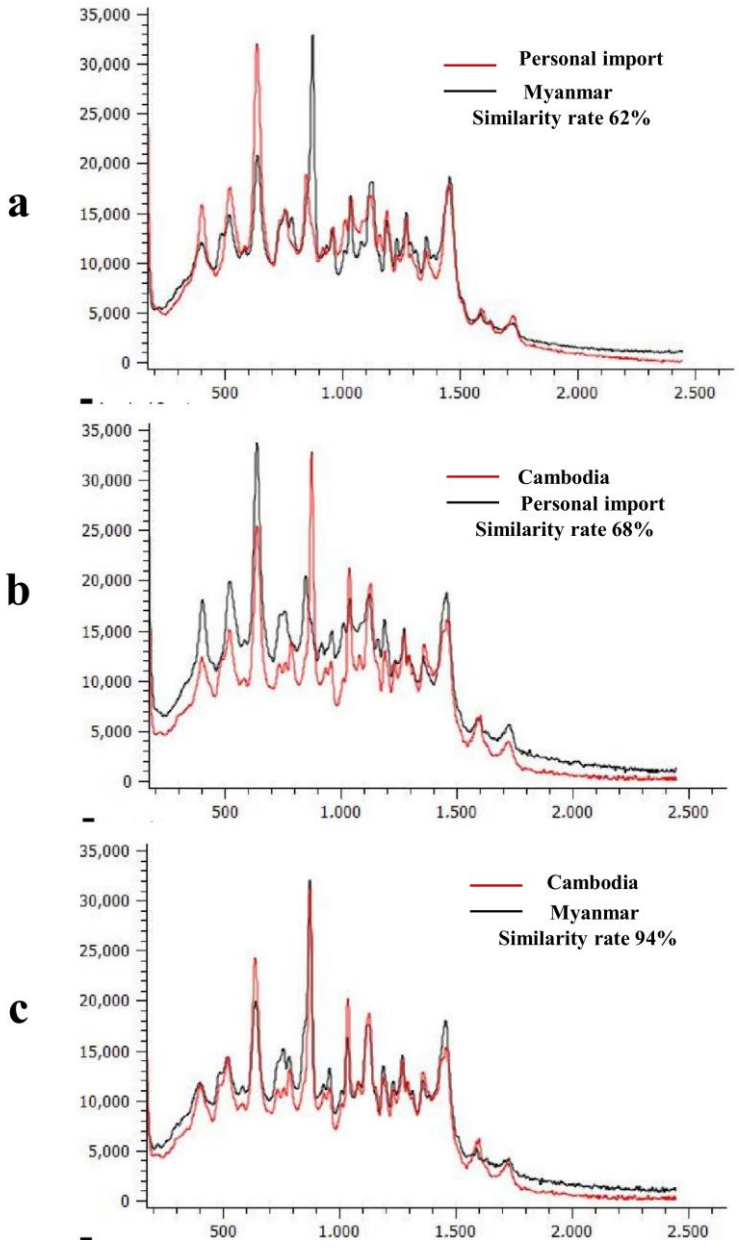

Figure 3.2: Raman spectroscopy of samples from manufacturer X. a) Personal import and Myanmar products, b) Cambodian and personal import products, c) Cambodian and Myanmar products

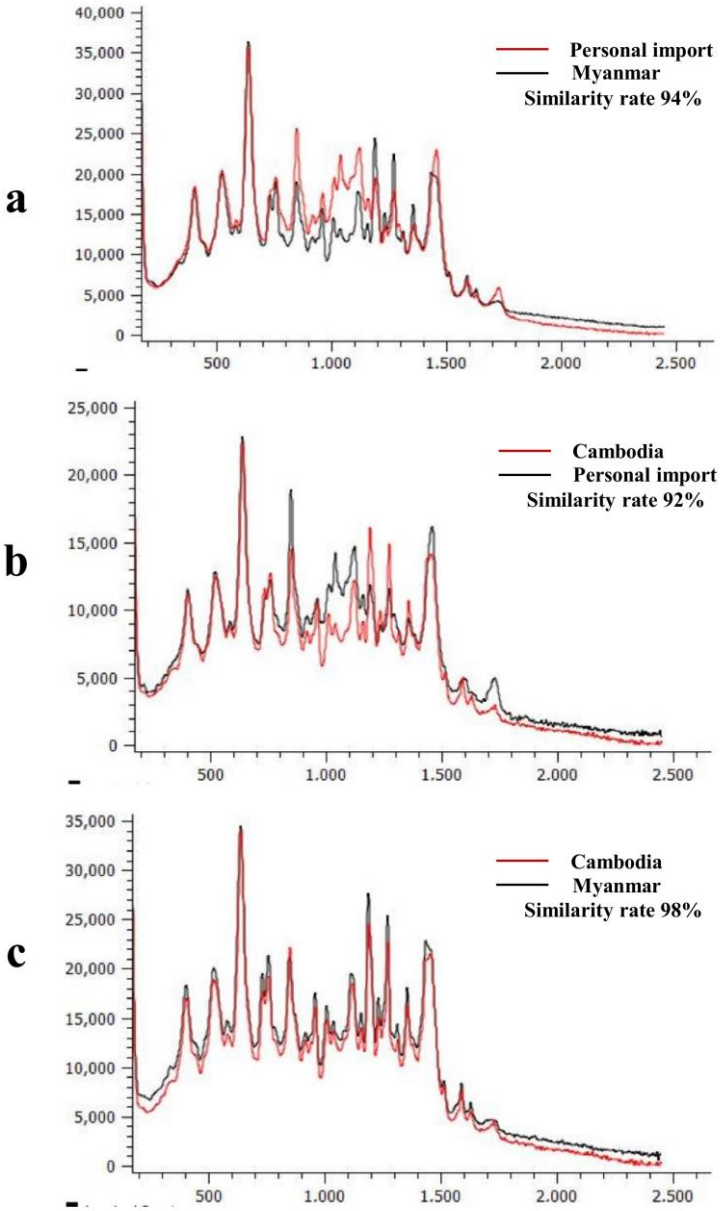

Figure 3.3: Raman spectroscopy of products from manufacturer Y. a) Personal import and Myanmar products, b) Cambodian and personal import products, c) Myanmar and Cambodian products

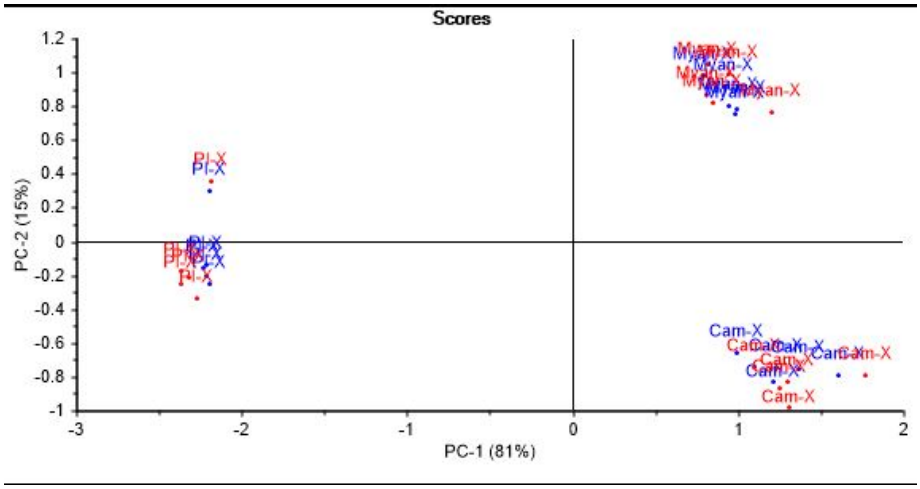

Figure 3.4: PCA score plot for Cambodia, Myanmar, and personal import samples of manufacturer X

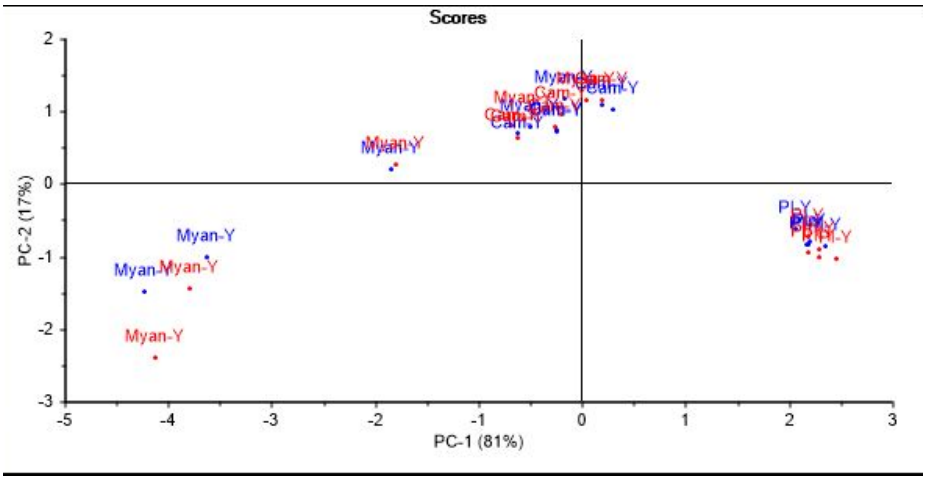

Figure 3.5: PCA score plot for Cambodia, Myanmar, and personal import samples of manufacturer Y

3.4. Discussion

The quality of omeprazole purchased through the internet and imported into Japan for personal use have mostly passed in quantity and content uniformity tests, and all the samples passed the dissolution test. However, many of the sites were selling omeprazole without prescription, though omeprazole is a prescription medicine in Japan. Some sites did not provide a physical address or contact number. Most importantly, one did not deliver the advertised product to the consumer. Illicit online shops do not necessarily provide detailed information about proper use of their products (Nielsen & Barratt, 2009; Wax, 2002). As has previously been noted, there was little response to our inquiries about product authenticity and legality (Khan et al., 2012, Khan et al., 2011). Thus, there is a clear risk to consumers who purchase products via the internet.

Another aim of this study was to assess whether there was a quality difference between the same products from the same manufacturer distributed in different countries. Indeed, we found that the quality of the products imported personally through the internet in Japan was much better than that of corresponding samples previously collected in Cambodia and Myanmar. In particular, omeprazole samples from two manufacturers, collected in Cambodia and Myanmar, failed dissolution tests, whereas the corresponding products delivered to Japan passed. For manufacturer X, the Raman-based difference in correspondence between personal import omeprazole and Cambodian or Myanmar omeprazole was 30–40% which was further supported by the PCA analysis (Figure 3.4). There was also a difference in the case of manufacturer Y, though it seemed smaller from Raman data but the PCA analysis demonstrated a clearly distinguishable variation of the samples (Figure 3.5). Although small variations in purity, size, strength, and other parameters are permitted, a difference of nearly 40% is unlikely

to be compatible with GMP (Good Manufacturing Practice) (FDA, 2017). It has been reported that some manufacturers intentionally produce substandard medicines in order to exploit regulatory loopholes for commercial gain (Buckley & Gostin, 2013; Caudron et al., 2008; Johnston & Holt, 2014). We cannot rule out the possibility that this occurred in the present case, although it should be borne in mind that other factors, such as improper storage conditions in the distribution chain, might have contributed to the properties of the medicines.

A limitation of this study was the relatively small number of the samples and the internet sites from which samples were collected. Nevertheless, we were able to identify suspicious sites and suspicious samples. Another limitation was the low response rate in authenticity investigation, highlighting the need for better cooperation from manufacturers and regulatory authorities.

3.5. Conclusion

Omeprazole formulations are readily available online with or without a prescription. The quality of omeprazole purchased via the internet and personally imported into Japan was mostly passed in quantity and content uniformity tests, and all the samples have passed in the dissolution test. Nevertheless, the same products from some of the same manufacturers, previously collected in surveys in Cambodia and Myanmar, had proved unsatisfactory, especially as regards dissolution properties. Further investigation is needed to establish whether some manufacturers are intentionally producing substandard medicines for sale in certain market segments, or whether other factors are involved.

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Chapter 4

Public health concerns of substandard antidiabetic medicine: Quality estimation of pioglitazone by a cross-sectional survey

4.1. Introduction

There is evidence that both falsified and substandard medicines are a threat to the public health. In addition to major economic losses, these poor quality medicines make the patients suffer by prolonging sickness, which may lead to death (Tabernero et al., 2015; Khan et al., 2013). Poor quality medicines may take several forms, one of them of which is substandard medicines according to Newton et al (Newton et al., 2011). The problem of substandard medicine has been persistent over a long period of time (Almuzaini et al., 2013; Caudron et al., 2008; Khurelbat et al., 2014) and the issue of substandard medicine is being overshadowed while the drug quality monitoring authorities are largely focusing on drug falsification (Katsnelson, 2010; Bate et al., 2008). The exact figure of the substandard medicine is difficult to ascertain because of the insufficient methodological study and reporting systems. According to a review by Caudron et al. the percentage of substandard medicine in several Asian and African countries is 8-46% (Caudron et al., 2008). A similar study in six African countries revealed that 35% of their total collected samples were substandard (Bate et al., 2008).

Moreover, with the rise of e-commerce, situation of substandard medicine is being aggravated by the online pharmacies. This new trading system which has now become an integral part of life for a variety of uses has made drug sub-standardization profitable and alluring to the unethical manufacturers (Mackey et al., 2016; Fittler et al., 2013). Nowadays it is not uncommon for patients to buy medicines online with or without consulting physicians. Approximately 60% of internet users in some developed countries, such as Japan and the USA, use the internet for their health related activities (Khan et al., 2012). There is an increased risk that this international trade in pharmaceuticals via sales on the internet will facilitate the entry of these poor quality products into the legitimate

supply chain. Regardless of this threat, as of now there was no published data on the quality of pioglitazone from China or Myanmar. China and Myanmar were of special concern as China is the second producer, after India, of most falsified or substandard medicines in the global market and the recent situation of Myanmar was unknown (Pan et al., 2016).

Pioglitazone, a relatively new class of oral hypoglycemic agent, is one of the widely used drug for the treatment of Type-2 diabetes mellitus since its approval in 1999 as an adjunct to exercise and diet to improve glycemic control in adults with type 2 diabetes mellitus (Shukla & Kalra, 2011). It is sold in the market as a single product under the brand name Actos or in combination with metformin (Actoplus Met, Actoplus Met XR) and glimepiride (Duetact) (Richter et al., 2006; FDA, 2011).

This research study was undertaken to address the aforementioned concerns and provide data of good methodological quality to accurately determine the quality of pioglitazone in China and Myanmar along with the pioglitazone sold online for personal use. This information will be of value to public health officials and pharmaceutical practitioners to reliably determine the extent of the problem, and then can serve as a valid comparison for future studies to evaluate interventions to improve the drug supply quality. It will also help guide further research to better understand the health impact of poor quality medications in these countries.

Box 4: Summary of Chapter 4

- **Research focus**

➢ Evaluation of the quality of pioglitazone tablets collected from Myanmar and China as well as from the internet sources and personally imported into Japan.

- **Key findings**

➢ Online sites selling pioglitazone without restriction and approval is of great concern.

➢ Substandard pioglitazone formulations are circulating in the pharmaceutical market of Mandalay, Myanmar.

➢ Substandard pioglitazone formulations for personal use are also available from the internet sources.

➢ Quality of pioglitazone from Shanghai was apparently satisfactory.

- **Strengths and limitation of the study**

➢ Samples from Shanghai were collected from the authentic sources with prescription. The quality test results might vary with different sample collection methods and analysis methods in different pharmacopoeias, so care is needed in comparing these results with others.

4.2. Methods

4.2.1. Study design and sample collection

Using cross-sectional sampling, samples (N = 163) were collected from the following sources: (a) hospitals in Shanghai, China in 2012; (b) personal purchases of products via internet and imported into Japan in 2013; and (c) Mandalay, Myanmar in

2015. Samples were collected from Huangpu District and Pudong New Area of Shanghai, China between October and December in 2012. Personally imported samples from internet sources were collected during the time period of September and December in 2013. Google Japan was used as a search engine and the search term was 'ピオグリタゾン AND 個人輸入' for Japanese language site and 'Pioglitazone and personal import' for English language site. Samples from Myanmar were collected from Mandalay region during September to October 2015.

4.2.2. Sample analysis

Sample analysis consisted of observation test, authenticity investigation, legality investigation, registration and pharmacopoeial analysis.

4.2.2.1. Observation test

Each sample was given a distinct code after receiving the shipment. Details of the packaging condition and label information were noted carefully. During observation, focus was given to the packaging and labeling, physical appearance of the tablet, their size, shape, color etc. according to the WHO guideline and FIP checklist for visual inspection of medicine (WHO, 1999; FIP, 2012) (Appendix 2). For personal import samples shipping to Japan from internet pharmacy, the sites were observed if it follows the Pharmaceutical Affairs Law (PAL) of Japan (MHLW, 1960; MHLW, 2011; MHLW, 2013).

4.2.2.2. Authenticity and legitimacy investigation

For the authenticity investigation, a detailed questionnaire of the sample was sent to the respective manufacturer and the manufacturing country to confirm the authenticity of their product and the legitimacy of the manufacturer (Appendix 3, 4, 5, & 6). Each

questionnaire consisted of a detailed information of the product for example- manufacturer name, batch number, manufacturing and expiry date, dosage and strength of the product as was indicated by WHO (Khan et al., 2012; WHO, 1999). Registration status of the all the product was evaluated by visual inspection of the packaging and then sending a questionnaire to importing country to confirm the registration of the product (Appendix 7 & 8).

4.2.3. Quality test

4.2.3.1. Materials

Pioglitazone hydrochloride as the reference standard, Benzophenone as an internal standard, methanol, acetonitrile, ammonium acetate, potassium chloride and other chemicals of reagent grade were procured from the Wako Pure Chemical Industries Ltd. Japan. Hydrochloric acid was purchased from Nacalai Tesque Inc. and acetic acid was purchased from Alfa Aesar.

4.2.3.2. HPLC analytical procedure of the samples

Analysis of the sample was done according to the modified and validated JP (Japanese Pharmacopoeia) indicated protocol and performed using HPLC (High-Performance Liquid Chromatography) (JP, 2012; JP, 2016). HPLC analysis was carried out at 269 wavelengths in a Prominence HPLC Shimadzu (Photo Diode Array Detector, SPD-20A/20AV Series) with Phenomenex Gemini NX C18 column (150 x 4.6 mm). Flow rate, injection volume, and detection wavelength were kept identical throughout the entire analysis. The dissolution test was performed with an NTR-VS 6P dissolution apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan). Drug release studies were carried out by the USP Type II paddle method. The paddle was set to rotate at 50 rpm for 45 minutes and the temperature was maintained at 37 ±0.50 ºC. Standard solutions were prepared by

dissolving accurately weighed quantities of Pioglitazone Hydrochloride (reference standard) and Benzophenone (internal standard) in the diluent to obtain solutions with concentrations of 0.2 mg/mL and 0.1 mg/mL, respectively. Several dilutions were made to bring the final concentration of 0.025 mg/ml. The concentration of the test solution was kept to 0.1 mg/ml. The relationship between the peak area and concentration of each reference standard was linear within the range of 25–200% of the active ingredient (r^2 = 0.999–1.000), and the quality test was performed within that range.

4.2.3.3. Acceptance criteria

In the pharmacopoeial test, identification (BP, 2010; USP, 34; JP, 2012; JP, 2016), quantity, content uniformity, and dissolution acceptance criteria of the pioglitazone HCl tablets were as follows-

- **Identification test**

The retention time of Pioglitazone peak of the sample solution should correspond to that of the standard solution.

- **Assay**

Pioglitazone HCl tablets contain the equivalent of not less than 95.0% and not more than 10.5.0% of the labeled amount of pioglitazone.

- **Content Uniformity**

In the first stage, acceptance value of 10 tablets should be equal to or less than 15. In the 2nd stage, AV of 30 units should be ≦ 25 and no individual content is less than [1-(0.01*L1)]M or more than [1+(0.01*L1)] M. Calculation of acceptance value (AV); AV= |M-x̄ | + KS where, M: reference value; x̄: mean of individual contents; K:

acceptability constant, K=2.4 when the number of unit is 10, and the K=2 when the number of unit is 30; S: standard deviation of the sample.

- **Dissolution test**

In dissolution test, after 45 minutes in the dissolution medium in 1st stage the percent release of 6 individual tablet should be not less than Q+5% (Q=80%); in the 2nd stage, average value of 12 units should be greater than or equal to Q & no unit should be Q-15% (Q=80%); and in the 3rd stage, average value of 24 units should be greater than or equal to Q, not more than 2 units should be less than Q-15% & no unit should be less than Q-25% (Q=80%).

4.3. Results

A total of 163 samples were collected for this study. Among these, n=44 samples were from Shanghai, China, n=60 sample from Mandalay, Myanmar and n=59 samples were from internet sources and personally imported samples to Japan. The details of the sample location and number of samples along with their strength are outlined in Table 4.1.

4.3.1. Observation of the samples and the online sites

No unusual or suspicious information was found for any sample during visual inspection of the samples except for two samples from one manufacturer where two different batch numbered strips were found in one box. The physical appearance of the samples was also acceptable. However, some serious issues like selling medicines without prescription or delivering the different amount of ordered tablets were observed for the online sites during purchase of samples for personal import. Among the 32 online site

visited to buy 59 samples, some online sites seemed not to follow the required regulation. Site observation result of online pharmacies is outlined in Table 4.2.

Table 4.1: Outline of the samples by sampling site, category and strength

Sampling Site	Year	Category	Strength			
			15 mg	30 mg	45 mg	Total
Shanghai, China (Chang, 2014)	**2012**	**Brand**	9	-	-	44
		Generic	35	-	-	
Personal import samples	**2013**	**Brand**	19	4	5	59
		Generic	19	9	3	
Mandalay, Myanmar	**2015**	**Brand**	1	-	-	60
		Generic	59	-	-	
Total number of samples			n = 163			

Table 4.2: Online sites observation result

Category	Number of sites (n=32)
Site without any physical address	6 (18.8%)
Site without contact number	13 (40%)
Site without purchasing amount restriction	14 (43.8%)
Site without prescription requirement	32 (100%)
Site without approval of selling 45 mg Pioglitazone in Japan	4 (12.5%)
Site delivering different amount of tablets ordered	4 (12.5%)

4.3.2. Authenticity investigation

Each manufacturer and the manufacturing country was sent request along with the questionnaire to verify the authenticity and legitimacy of the product and manufacturer

respectively. But the authenticity of the product and legitimacy of the manufacturer remained unclear as there was a little response from the manufacturer as well as from the manufacturing country. Those who replied who replied confirmed their sample to be genuine. In the case manufacturing country, the best response was found for the personal import samples where 5 out of 7 manufacturing country ensured that these manufacturers had the approval to manufacture pioglitazone product. Results of authenticity investigation is given in Table 4.3.

Table 4.3: Authenticity investigation

Category		Replies (total number)	Reply on samples (number of samples)	Authentic		
				Yes	No	Unknown
China (Chang, 2014)	**Manufacturer**	1 (9)	9 (35)	✓		
	Manufacturing country	1 (2)	9 (35)	✓		
Personal import samples	**Manufacturer**	1 (11)	28 (59)	✓		
	Manufacturing country	5 (7)	37 (59)	✓		
Myanmar	**Manufacturer**	2 (6)	9 (60)	✓		
	Manufacturing country	1 (4)	1 (60)	✓		

4.3.3. Quality test result

After the final assessment, quality test results of the sample from Shanghai was found satisfactory where only 1 sample failed to meet the pharmacopoeial requirement. The average quantity of API (active pharmaceutical ingredient) in all the samples was 98.1%±2.7 (mean±SD) of label claim and the acceptance value (AV) for uniformity of

content of all samples was below 15. However, in the case of samples from Myanmar and personal import, dissolution of the pioglitazone tablet in the dissolution medium was the main concern. For personal import, 38% generic samples were found to be failed among the 13 samples analyzed.

Table 4.4: Summary of the quality test results of pioglitazone hydrochloride

Sampling Site	Year	Test	Test n (%)				
			Brand		Generic		Total samples
			Pass	Fail	Pass	Fail	
China (Shanghai) (Chang, 2014)	**2012**	**Quantity**	9 (100)	0 (0)	34 (97)	1 (3)	44
		Content Uniformity	9 (100)	0 (0)	35 (100)	0 (0)	
		Dissolution	9 (100)	0 (0)	35 (100)	0 (0)	
Personal import samples	**2013**	**Quantity**	19 (100)	0 (0)	13 (100)[5]	0 (0)[6]	59
		Content Uniformity	19 (100)	0 (0)	13 (100)[7]	0 (0)[8]	
		Dissolution	19 (100)	0 (0)	8 (62)[9]	5 (38)[10]	
Mandalay, Myanmar	**2015**	**Quantity**	1 (100)	0 (0)	59 (98)	1 (2)	60
		Content Uniformity	1 (100)	0 (0)	59 (98)	1 (2)	
		Dissolution	1 (100)	0 (0)	51 (86)	8 (14)	
Total number of samples			**n = 163**				

[5] Among the 31 generic samples, tests were done only for 13 samples as there was not enough tablets to conduct the full test.

[6] See supra note 5

[7] See supra note 5

[8] See supra note 5

[9] See supra note 5

[10] See supra note 5

In Myanmar 2015, among the collected 60 samples 13.3% samples were found to be failed. Summary of the quality test results is shown in Table 4.4 and the details of the quality test results of pioglitazone from Myanmar 2015 are presented in Appx 14-16.

The average percent release of the passed samples in the dissolution medium was 95.0±3.9 (mean±SD) and the average percent release of each failed sample is presented in Table 4.5. Drug release studies of the failed samples for a longer period of time indicated that they did not meet the threshold requirement of time to be dissolved in the dissolution medium and remained intact (Fig 4.1 and 4.2). Most of the tablet remained intact even without disintegrating in the dissolution medium (Fig 4.3 A and B). Overall, the quality test results of brand samples were quite satisfactory whereas generic samples raise a serious concern.

Table 4.5: Average percent release of the failed samples in dissolution test (Q= 80% of label claim in 45 minutes)

Sample source	Sample code	mean (%) release ±SD
Personal Import	23-GE-30-1	12.3±5.3
	25-GE-30-1	11.2±0.5
	31-GE-15-1	26.1±2.7
	16-PIO-15-2	61.09±2.6
	30-GE-30	60.3±2.2
Mandalay, Myanmar	A-032	67.0±7.6
	A-062	68.5±6.9
	A-079	47.6±5.8
	A-086	72.6±5.0
	B-015	67.3±10.0
	B-020	69.4±6.3
	B-107	71.2±11.5
	PA-013	62.0±5.2

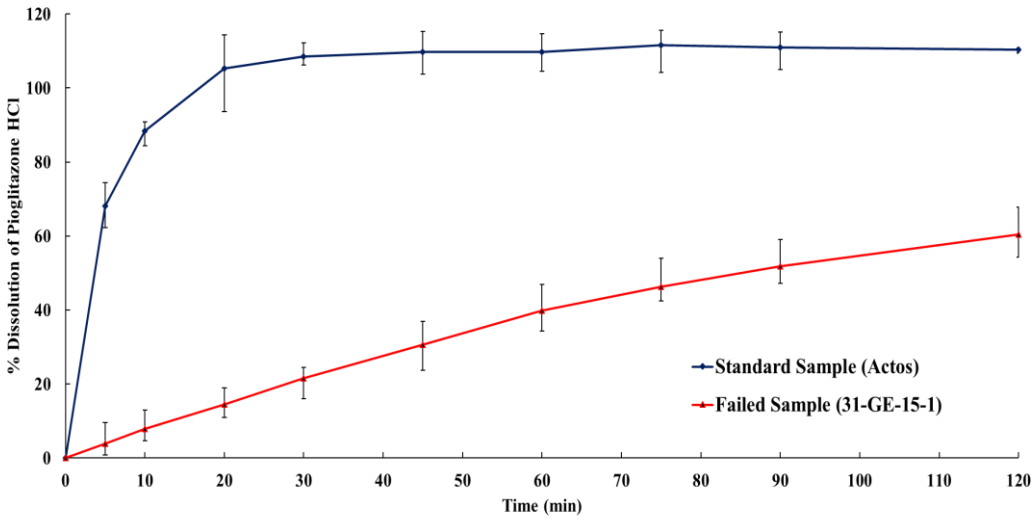


Figure 4.1: Dissolution profile of standard sample and failed personal import sample for 120 minutes (Q= 80% of label claim in 45 minutes)

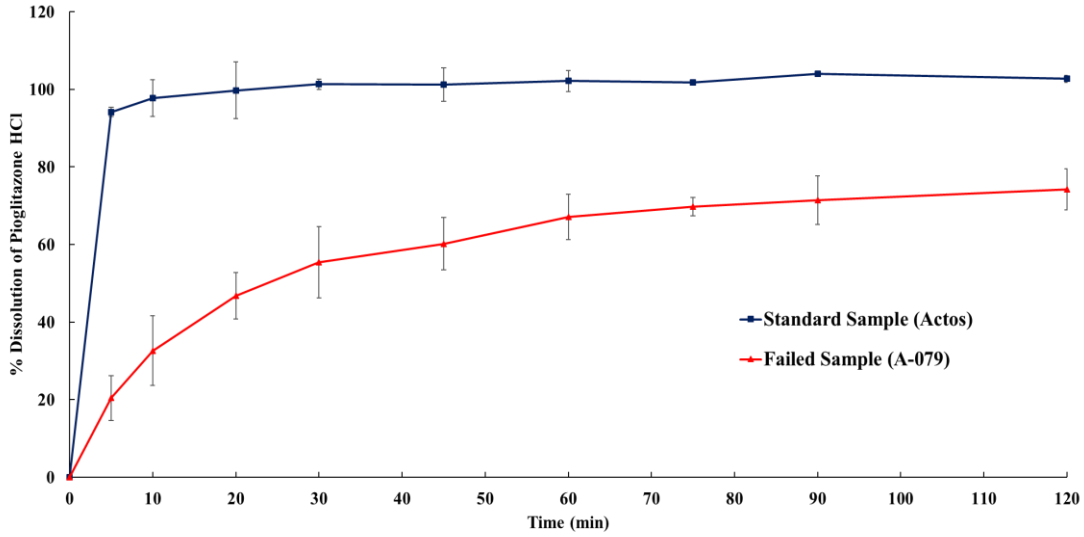
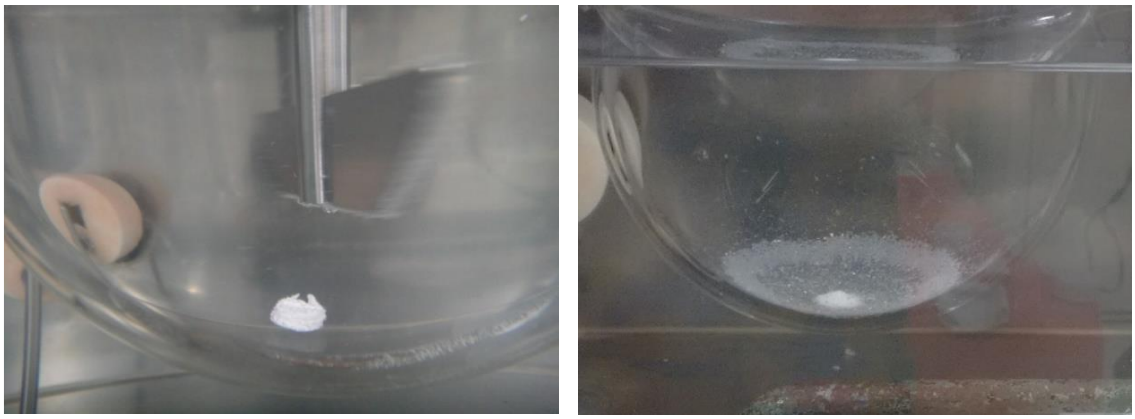


Figure 4.2: Dissolution profile of standard sample and failed Myanmar sample for 120 minutes (Q= 80% of label claim in 45 minutes)



A B

Figure 4.3: Undissolved tablet in the dissolution vessel. A) personal import sample and B) Myanmar sample

4.4. Discussion

Access to good quality medicines is a key component of the quality health system. This study finding indicates several problems that may hinder the access of diabetic patients to pioglitazone of reliable quality. Although our observation of the samples did not lead us to any unusual finding, careful observation of the online site has revealed some serious issues that should no longer be ignored. According to Pharmaceutical Affairs Law (PAL) in Japan selling of prescription drug without prescription is strictly prohibited (MHLW, 1960; MHLW, 2011; MHLW, 2013), but among the 32 site visited no online pharmacy required prescription to sell pioglitazone. Additionally, 45 mg pioglitazone is not approved to be sold yet 4 pharmacies were found to be selling 45 mg pioglitazone. 14 pharmacies were selling without any restriction in purchasing amount. Surprisingly, most of the samples found to be failed in quality test were purchased from

the site that did not reveal any physical address. In the case of Myanmar samples, all the samples collected for our study were of foreign origin which indicates that all of the needs of antidiabetic medicine is met by foreign manufacturers. This finding may indicate that when there are unmet needs from internal sources and a weak enforcement of regulations, medicines can enter the country through unauthorized channels. The authenticity of the product and legitimacy of the manufacturer remained unclear as there was a little response as observed previously (Khan et al., 2010; Khan et al., 2011). In such a case, it can be assumed that the manufacturer is already aware of the distribution of low-quality products in the pharmaceutical market.

In our study, quality analysis of the sample from Shanghai, China was satisfactory where only 1 sample out of 52 sample failed to meet the pharmacopoeial requirement of API (active pharmaceutical ingredient). Our study suggests that quality of pioglitazone from Shanghai may not be that big problem as it's claimed or it is because the samples from Shanghai were collected from authentic sources using prescription (Khan et al., 2012; Delepierre et al., 2012; Kelesidis et al., 2015).

For imported and Myanmar pioglitazone samples, dissolution was the main problem where the tablets failed repeatedly to disintegrate and dissolve in the medium indicating the solubility problem. For personally imported pioglitazone from online sites, substandard pioglitazone amounted up to 8.5% of total sample collected. 3 personally imported samples failed seriously in dissolution test, drug release amount of which was below 30% (Table 4.5). For that three samples, no reliable comparator was available to be confirmed that these samples were falsified. For Myanmar sample the failure rate was even higher than the personal import samples, which was 13.3%. The dissolution profile of these failed samples indicated that they need much longer time to dissolve

properly in the medium. While the sample were crushed into powder form and allowed in the medium, percent dissolution was higher than the tablet.

In contempt of the apparent satisfaction about the quality of pioglitazone samples collected from China, substandard pioglitazone from internet and Myanmar was the key issue. The substandard antidiabetic medicine that would not have had any antidiabetic effect would have been a waste of patient's money. The internet pharmacies those are selling pioglitazone online without restriction and approval is also of great concern.

This study had limitations. Since the samples were collected by a cross-sectional method from a specific area, this result does not represent the actual situation of another region. In this study, we only focused on pioglitazone samples hence the findings cannot be translated for other medicines' scenario. We could not validate the regulatory status of our samples due to lower response rate from manufacturer and manufacturing country. The failure rate of drugs might vary greatly with different sample collection methods and analysis methods in different pharmacopeias, so the comparison between our results and others should be interpreted with caution.

4.5. Conclusion

Even though the evidence from study findings suggests that pioglitazone samples collected from China were of acceptable quality, substandard medicines may continue to be available in internet and Myanmar. In contempt of the apparent satisfaction about the quality of pioglitazone samples collected from Shanghai, substandard pioglitazone from internet and Myanmar was the key issue. These poor quality medicines failing to dissolve properly after ingestion will lead to ineffective treatment because of their lacking in

therapeutic efficacy and may pose great health risks to patients. Additionally, internet sites who do not follow the regulation may accelerate the circulation of the substandard pioglitazone. Therefore, reinforcing and maintaining the national and international regulatory oversight is needed to stop spreading the poor quality medicines.

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Chapter 5

The Health Consequences of Falsified Medicines: A Study of the Published Literature

5.1. Introduction

Falsified medicines may lead to avoidable morbidity, mortality, drug resistance, early death, or treatment failure, as well as loss of faith in health systems, especially in low-income and middle-income countries, and therefore a reliable supply of good-quality medicines is essential for public health (Kelesidis & Falagas, 2015; Newton et al., 2014). However, it has been difficult to quantify the impact on patients' health, because of fragmented and incomplete reporting of incidents and because the consequences of falsified medicines may range from no effect at all to enabling disease progression (Cheng, 2009), or to lethal toxicity, as in the case of diethylene glycol-containing cough syrup (Rentz, 2008; Hanif et al., 1995). Also, inadequate doses of anti-infectives may lead to drug resistance (Alfadl et al., 2008; Mackey & Liang, 2011).

With the exponential increase in internet connectivity, those engaged in distribution of falsified medical products have gained access to a global market place (Venhuis et al., 2014), and no country remains untouched by this issue. The growth of a culture of self-diagnosis and self-prescribing has led to the emergence of thousands of unregulated websites providing unsupervised access to medical products with no guarantee of authenticity (Cicero et al., 2012). Thus, what was once considered a problem suffered by developing and low-income countries has now become an issue for all, although low- and middle-income countries and areas of conflict or unrest are still most vulnerable to falsified medical products owing to inadequate health-related regulatory systems.

Falsified medical products are generally difficult to detect, as they are usually designed to appear identical to the genuine product and may not cause an obvious adverse reaction, although they may be ineffective. Falsification can be intentional, accidental, or due to negligence, and may involve medicines with no API (active pharmaceutical

ingredient), the wrong API, an inappropriate amount of API, potentially resulting in zero efficacy, some efficacy, or toxicity (WHO, 2010). It may involve diverted, re-labeled, re-packaged, or mixed products (WHO, 2017a). There is currently no universally agreed definition of what used to be widely known as 'counterfeit medicines' (WHO, 2017b). According to Newton et al., the term should be used to describe products that are deliberately and fraudulently mislabeled with respect to identity and/or source, including products with correct or incorrect ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging (Newton et al., 2010). The US FDA (United States Food and Drug Administration) definition includes products that may be contaminated or contain the wrong or no active ingredient, or the right active ingredient but at the wrong dose (US-FDA, 2017). The EU (European Union) includes products that might contain ingredients, including active ingredients, of poor quality or at the wrong dose, but pass themselves off as real, authorized medicines. The term "falsified" refers to all forms of falsification, while the term "counterfeit" specifically refers to an infringement of intellectual property rights. Falsifications are becoming more sophisticated (EU, 2017), and falsified medicines can be found in illegal street markets or obtained via unregulated websites, and have been detected even in pharmacies, clinics and hospitals (Buckley & Gostin, 2013).

The purpose of this research is to study the literature describing the health consequences of falsified medicines, focusing on mortality and morbidity, as well as the scale of the issue, the geographic extent, the medicines affected, and the harm caused at both the individual and population levels. We do not attempt to present an exhaustive

analysis of every health consequence of substandard or falsified drugs, but aim to give an overview of the actual impact of these products on public health.

Box 5: Key points of Chapter 5

- PubMed was searched to identify reports about the effects of falsified medicines.
- A total of 82 English-language articles were identified, categorized, and tabulated the data.
- All types of medications have been falsified, affecting both children and adults.
- Numbers of incidents were similar in developing and developed countries.

5.2. Methods

This study of the literature is based on searches performed in PubMed. Four authors (MSR, NT, JE, OM) independently performed the literature search, selection of relevant articles, and data extraction.

5.2.1. Stage 1

Initially, articles were hand-searched in PubMed using different combinations of key words to identify relevant articles, aiming to optimize keyword selection. The key words were "(counterfeit OR fake) AND (medicine OR drug) AND (problem OR safety OR threat OR victim OR hazard OR harm OR injury OR impact OR damage)". In addition, MeSH search was conducted using the keyword 'counterfeit' or 'fake'. We then examined

the search results for articles written in English that described the health impact and causes of falsified medicines.

5.2.2. Stage 2

Based on the results of Stage 1, we focused on the search words ‘‘(counterfeit OR fake OR bogus OR falsified OR spurious) AND (medicine OR drug)’’, because the terms ‘counterfeit’, ‘spurious’ and ‘falsified’ have been defined by WHO (WHO, 2017b), and the terms ‘bogus’ and fake’ were frequently found in connection with falsified medicine in the articles identified in Stage 1 (Lancet, 1924; Dondorp et al., 2004). Selection criteria for articles were the same as in Stage 1.

5.2.3. Stage 3

After consideration of the results from Stage 2, we next conducted a search of PubMed for the year 2010 using the various combination of keywords ‘‘(counterfeit OR fake OR bogus OR falsified OR spurious) AND (medicine OR drug)’’. This search hit 1700 articles in total, and a review of these articles yielded 11 describing health damage due to falsified medicine, 7 describing health damage not due to falsified medicine, and 18 not reporting health damage.

Keywords were extracted from the abstract of each of these articles using the IBM SPSS Text Analytics. Then, using the same keywords, the PubMed search result was compared with the results from other databases (Google Scholar, Scopus, Web of Science). For the same keywords, most of the relevant articles were picked up in the PubMed database, whereas more were missed in the other databases. Therefore, PubMed was selected the preferred database for the present purpose.

5.2.4. Data extraction criteria of the selected articles

Based on the above findings, a comprehensive search of PubMed was conducted on February 2013. Three additional searches were conducted between March 2013 and February 2017. The search term was ‘‘(counterfeit OR fake OR bogus OR falsified OR spurious) AND (medicine OR drug)’’. From the hits, we selected English language articles describing damage to patients’ health due to falsified medicines. When possible, primary sources (reporting the outbreak or case studies) have been cited; data from publications were included and tabulated if they provided examples of serious health hazards, adverse reactions, injury, or deaths. There were some articles among the searched articles in which the terms false, deliberate contamination or adulteration were used to describe apparently falsified drugs. Incidents described in these articles were judged as falsified medicine incidents and data from these articles were included.

5.2.5. Statistical analysis

Results are summarized as descriptive statistics and expressed as number and percent. Graphs were prepared using Microsoft Excel 2010. IBM SPSS Text Analytics 2013 version was used for the keyword selection.

5.3. Results and discussion

Among the 1,608 articles hit in the final search using the selected key words, English language articles with a full text amounted to 1477. The additional searches between February 2013 and February 2017 yielded 398 articles, of which 314 articles were full-text English language articles. These articles reported a total of 49 incidents related to falsified drugs (Table 5.1) describing 7200 causalities among which 3604 people died

(death rate 50.1%). In table 1, two cases were not included although there have been several reports (Cheng, 2209; Cockburn et al., 2005; Deisingh, 2005; Newton et al., 2006; Ziance, 2008; Wertheimer et al., 2003) that in 2001 alone, a total of 192,000 people died due to fake medicines in China, as first reported by a government-owned newspaper, Shenzhen Evening News (Fackler, 2002). Regarding this specific case, one of the Chinese official confirmed that the incidence of 192,000 peoples' death was mistakenly translated by a journalist where the reason was mentioned as due to falsified medicines. The second case was also in China where, diethylene glycol contamination of paracetamol syrup killed 192,000 people in 2002 (Jackson et al., 2010). However, no details were reported on specific drugs or therapeutic categories of drugs involved, although it is possible that second case refers to the same incident, as the reported number of people affected was the same. Some cases were regarded as duplicates, because health damage, occurrence year, country, drugs and cause were the same.

5.3.1. Geographical distribution of incidents

Among the total reported incidents involving health damage due to falsified medicines (n=49), 27 (55.1%) occurred in developing countries. The other 22 (44.9%) incidents have occurred in developed countries (World Bank, 2017). The distribution of these incidents among regions is shown in Fig 5.1. The 2006 estimate of falsified medicines by WHO indicated that the prevalence of falsified medicines ranged from less than 1% in developed countries to over 10% developing countries (WHO, 2006). But, it is noteworthy that our results show that the difference between developing and developed countries is quite small in terms of the number of incidents where falsified pharmaceuticals actually impacted on human health.

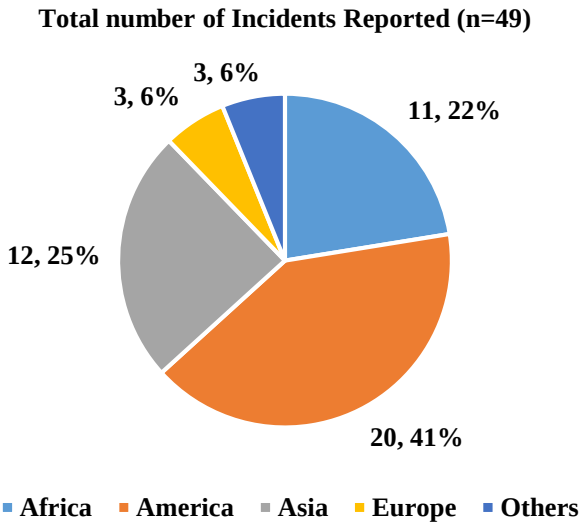

Figure 5.1: Prevalence of the health damage incidents by region. (Others= Australia, unknown)

What was once regarded a problem mostly affecting developing and low-income countries now seems a serious issue for all (WHO, 2017). Surprisingly, the USA alone accounted for 25% of the total incidents reported. Since 2001, at least 10 drug falsification incidents affecting patients were reported, although the US-FDA suggests that drug counterfeiting occurs less frequently in the U.S. than in other countries due to their strict regulatory framework (US-FDA, 2017). This strict framework may mean that incidents are reported in the US that would have been overlooked or not reported in other countries with less well developed heath systems.

Incidents were also reported in other developed countries: Australia, Canada, Singapore, UK, Japan, Russia, and Norway. Among developing countries, Nigeria was the victim of repeated incidents of harm caused by falsified drugs, with the latest (falsified phenobarbital) being reported in 2014 (Table 5.1).

Among other developing countries, 2500 people died in Niger after receiving fake meningitis vaccine. Another report mentioned the death of 700,000 people due to fake anti-malarial and tuberculosis drugs, but gave no details as to the country involved, or the year (Table 5.1, case 48). There were also several cases for which enough details were not found to categorize it specifically as in case 42 of Table 5.1, where the sequence of supply chain was not clear to confirm if it was a medication error or the IV fluid was deliberately mislabeled. In a usual condition, simulated IV fluid for educational purpose is not entitled to be used for regular patients.

Table 5.1: Summary of incidents of falsified medicines causing health damage, including deaths or adverse reactions. In some cases, different numbers of injuries in the same incident were given in different articles. In cases where multiple articles give the same number, that number is shown; otherwise the maximum reported number of injuries for each incident is shown.

S.N.	Occurrence Year	Country	Health Impact	Cause	Reference(s)
01	1969	South Africa	7 children died	Diethylene glycol poisoning from sedative mixtures	Bonati, 2009; Alkahtani et al., 2010; Bowie, 1972
02	1982	USA	7 people died	Cyanide-laced paracetamol	Cockburn et al., 2005
03	1986	India	14 patients died	Receiving doses of impure glycerin contaminated with diethylene glycol	Pandya, 1988; Gautam et al., 2009
04	1988	Nigeria	A 21-year-old woman died	Hyperglycemia due to fake insulin	Cheng, 2009
05	1989	Haiti	89 people died	Paracetamol cough syrup prepared with diethylene glycol	Cohen et al., 2007
06	1990	Nigeria	109 children died	Acute renal failure from diethylene glycol contaminated syrup/elixir	Alfadl et al., 2013; Bonati, 2009; Alkahtani et al.,

					2010, Cockburn et al., 2005; Gautam et al., 2009; ten Ham, 1992; Okuonghae et al., 1992; Alubo, 1994; Stearn, 2004; Deisingh, 2005; Garuba et al., 2009; Hellstrom, 2011; Oshikoya & Senbanjo, 2010; Hall et al., 2006; Newton et al., 2006a; Reidenberg & Conner, 2001; Roger & Boateng, 2007
07	1990	Bangladesh	236 patient died including 51 children	Paracetamol syrup tainted with diethylene glycol	Hanif et al., 1995; Bonati, 2009; Alkahtani et al., 2010; Cockburn et al., 2005; Gautam et al., 2009; Hall et al., 2006; Newton et al., 2006a; Reidenberg & Conner, 2001; Roger & Boateng, 2007; Manchester, 2005
08	1992	Argentina	26 people died	Consumption of a propolis syrup with high level of diethylene glycol	O'Brien et al., 1998; Alkahtani et al., 2010; Cockburn et al., 2005; Gautam et al., 2009; Newton et al., 2006a; Reidenberg & Conner, 2001; Roger & Boateng, 2007
09	1995	Haiti	85 children died	Ingestion of paracetamol syrup adulterated with diethylene glycol	Alfadl et al., 2013; O'Brien et al., 1998; Bonati, 2009; Alkahtani et al., 2010; Cockburn et al., 2005; Stearn, 2004; Deisingh, 2005; Hall et al., 2006;

					Newton et al., 2006a; Reidenberg & Conner, 2001; Roger & Boateng, 2007; CDC, 1996; Junod, 2000; Rassool, 2004; Wertheimer & Santella, 2005; Burki, 2010; Ziance, 2008; Wertheimer, 2003; Baratta et al., 2012; ten Ham, 2003
10	1995	Niger	2500 people died	Counterfeit meningitis vaccine	Alfadl et al., 2013; Stearn, 2004; Rassool, 2004; Wertheimer & Santella, 2005; Burki, 2010; Ziance, 2008; Baratta et al., 2012; Mukhopadhyay, 2007; Nsimba, 2008; Wertheimer & Norris, 2009; Reynolds & McKee, 2010
11	1998	Brazil	200 unwanted pregnancies	Dummy contraceptive pill	Stearn, 2004; Deisingh, 2005; Reidenberg & Conner, 2001; Wertheimer & Santella, 2005; Ziance, 2008; Wertheimer et al., 2003; Csillag, 1998
12	1998	India	36 children suffered acute renal failure, 33 of them died	Cough expectorant contaminated with diethylene glycol	Bonati, 2009; Alkahtani, et al., 2010; Cockburn et al., 2005; Gautam et al., 2009; Deisingh, 2005; Hellstrom, 2011; Hall et al., 2006; Newton et al., 2006a; Reidenberg & Conner, 2001; Roger & Boateng, 2007; Rassool, 2004; Mukhopadhyay, 2007; Kumar, 2001; Singh et al.,

					1998; Hari et al., 2006
13	1998	Brazil	Several people died	Dummy anticancer drug	Reidenberg & Conner, 2001; Csillag, 1998
14	1998	Russia	1000 patients were hospitalized	Counterfeit insulin	Ziance, 2008
15	1999	Cambodia	30 people died	Counterfeit artesunate prepared with suphadoxine-pyrimethamine	Roger & Boateng, 2007; Rassool, 2004; Mukhopadhyay, 2007
16	1999	USA	17 deaths and 254 with adverse effects	Counterfeit gentamicin	Moken, 2003
17	2001	USA	Several patients suffered tissue swelling or skin rashes in seven states	Injection of fake growth hormone	Editorial, 2001
18	2002	USA	A 16-year-old boy suffered painful spasms	Injection of diverted drug containing very low amount of epogen	Dooley et al., 2010
19	2002	USA	A cancer patient died	Counterfeit Procrit	Lawler, 2009
20	2004	Nigeria	3 hospitals reported cases of adverse reaction	Infusion contaminated with microorganism	Garuba et al., 2009
21	2004	Canada	4 people died	Heart attacks and strokes after taking Norvasc copycats made from pressed talc	Teichman, 2007
22	2004	Argentina	2 woman died and one gave premature birth to 26 week premature baby	Counterfeit iron injection for anemia	Stoneman et al., 2011
23	2005	USA	5 men died	Ingestion of misbranded dextromethorphan	Ziance, 2008
24	2005	USA	Respiratory paralysis of several people	Fake version of Botox	Liang, 2006
25	2005	Myanmar	A 23-year-old man died from cerebral malaria	Artesunate tablet containing paracetamol as a main ingredient	Newton et al., 2006b; Atemnkeng et al., 2007
26	2006	Canada	4 people died	Unauthorized substitution of counterfeit viagra containing talcum powder	Cheng &, Shaughnessy, 2008
27	2006	Panama	200 people died including more than 100 children	Paracetamol cough syrup contaminated with diethylene glycol	Rentz et al., 2006; Alfadl et al., 2013; Reynolds & McKee, 2010; Seiter, 2009; Marini et al., 2010
28	2007	Canada	A 58-year-old woman	Counterfeit zolpidem and acetaminophen	Teichman, 2007; Cheng &,

			died		Shaughnessy, 2008; Jackson et al., 2012
29	2007	Hong Kong	10 non-diabetic patients were hospitalized due to hypoglycemia including 1 death and another taken to ICU	Herbal drug for erectile dysfunction; (yellow capsules labeled as 假偉哥 and red/pink capsules named as "Nangen") containing glibenclamide	Kao et al., 2009
30	2008	China	12 patients died	Armillarisin manufactured with diethylene glycol as a solvent	Alkahtani et al., 2010; Lin et al., 2008
31	2008	USA	785 adverse reaction reports including 81 deaths	Counterfeit heparin contaminated with oversulfated chondroitin sulphate	Alfadl et al., 2013; Editorial, 2008; Lewis, 2009; Labadie, 2012
32	2008	Singapore	150 patients were hospitalized, 7 remained comatose and 4 subsequently died.	counterfeit Cialis (tadalafil), three herbal preparations and sildenafil	Hellstrom, 2011; Kao et al., 2009; Sugita & Miyakawa, 2010; WHO, 2010; Liang & Mackey, 2012
33	2008	Norway	44 people were suffering from poisoning	Fake flunitrazepam tablets containing scopolamine	Vallersnes et al., 2009
34	2008	Nigeria	118 children died	Paracetamol teething mixture containing diethylene glycol	Bonati, 2009; Alkahtani et al., 2010; Oshikoya & Senbanjo, 2010; Reynolds & McKee, 2010; Seiter, 2009
35	2009	China	2 people died	Counterfeit glibenclamide 6 times more potent than normal	Cheng, 2009; Lewis, 2009; Holzgrabe & Malet-Martino, 2011
36	2010	Australia	A 54-year-old man s suffered severe hypoglycemia	Ingestion of counterfeit Cialis	Chaubey et al., 2010
37	2010	China	81 patients were suffering from intraocular inflammation	Endotoxin-contaminated counterfeit Bevacizumab	Sun et al., 2011; Wang et al., 2013
38	2013	Guinea-Bissau	74 patients had recurrence or increased frequency of seizures, 2	Falsified phenobarbital	Otte et al., 2015

			subsequently died		
39	2014	Unknown	A 65-year-old male suffered hepatotoxicity	Chinese herbal medicine containing sildenafil	Nissan et al., 2016
40	2014	Nigeria	105 patients had increased frequency of seizures	Falsified phenobarbital	Otte et al., 2015
41	2014	Congo	930 people suffered dystonic reactions, 11 among them died	Falsified diazepam containing haloperidol	Peyraud et al., 2017
42	2014	USA	40 patients suffered adverse events including one death.	Non-sterile simulated IV fluids containing large amounts of endotoxin and significant bacterial contamination	Torrie et al., 2016
43	2015	USA	8 people suffered adverse effects	Ingestion of counterfeit alprazolam tablets found to contain fentanyl and, in some cases, etizolam	Arens et al., 2016
44	2015	India	15 patients suffered intraocular inflammation	Injections of counterfeit bevacizumab	Stewart et al., 2016
45	2016	USA	7 people suffered adverse effects	Norco (acetaminophen and hydrocodone), containing fentanyl and promethazine.	Vo et al., 2016
46	Unknown	UK	Acute lead intoxication in one man	Falsified ayurvedic drug for erectile dysfunction (Kamagra)	Barber & Jacyna, 2011
47	Unknown	USA	A child complained of burning sensation after injection with human growth hormone	Human growth hormone containing inexpensive insulin	Vastag, 2003
48	Unknown	Unknown	700,000 deaths	Counterfeit malaria and tuberculosis drug	Alfadl et al., 2013; Mackey & Liang, 2011
49	Unknown	Japan	A 39-year-old man was suffering from hypoglycemia	Sexual enhancement medication containing extremely large amount of glibenclamide and a small amount of sildenafil	Kuramoto et al., 2015

5.3.2. Therapeutic category

Among the categories of falsified drugs that caused health damage, sedatives, hypnotics, narcotics and, drugs for sexual dysfunction were the most common in both developing countries and developed countries. On the other hand, patients from developing or underdeveloped countries were mainly affected by falsified antipyretics, analgesics, and antitussives, such as paracetamol elixir, cough syrup, or teething mixture containing diethylene glycol (Alkahtani et al., 2010; Lin et al., 2008). Unfortunately, reports of very large numbers of deaths (Table 5.1, case 49) gave very few details, and could not be verified. Overall, the number of incidents by drug therapeutic category is illustrated in Fig 5.2.

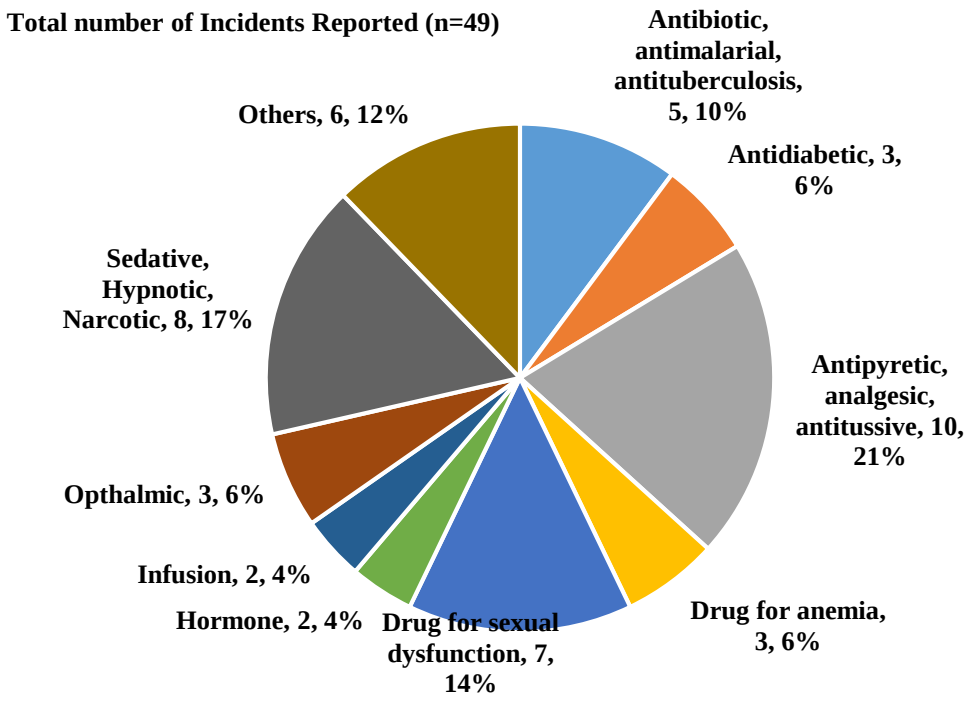

Figure 5.2: Number of incidents by drug therapeutic category. (Others=Anticancer, anticoagulant, antihypertensive, contraceptive, infusion, skincare, vaccine, etc.)

5.3.3. Annual trends in number of incidents and number of persons affected by falsified medicines

According to the PSI, the global incidence of drug counterfeiting has increased by 51% between 2011 and 2015, with 2015 seeing the highest level of counterfeiting to date, a 38% increase compared with 2014. The Institute documented 3,002 incidents of pharmaceutical crime during 2015 alone (PSI, 2017). Regarding health damage from falsified drugs, Fig 5.3 shows the numbers of incidents during various time periods.

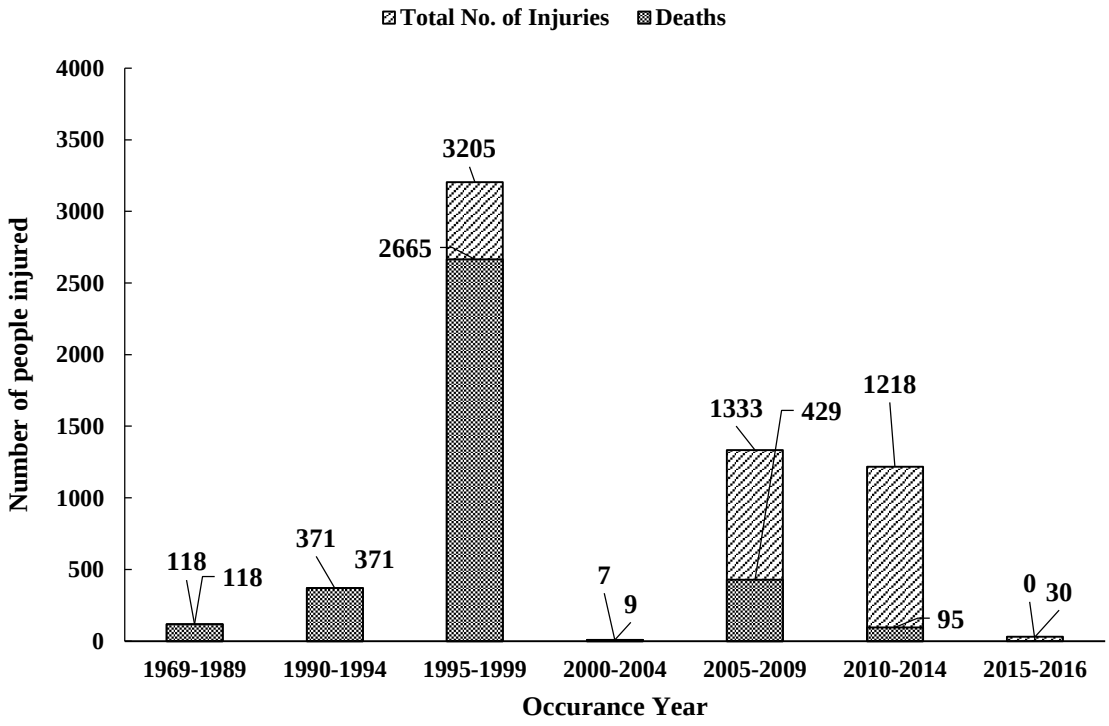

Figure 5.3: Yearly cases of health damage caused by falsified medicine (n=41). A total of 8 cases were not included to the chart as there was no clear indication of occurrence year (n=3), location (n=2), number of injuries (n=4), or medicine involved (n=2)

On the other hand, Fig 5.4 shows the numbers of persons affected during various time periods. No clear trends can be seen in either the number of incidents (Figure 3) or the numbers of people affected (Figure 4), although it is important to note that these figures exclude cases where insufficient information was available in published reports (see figure legends for details).

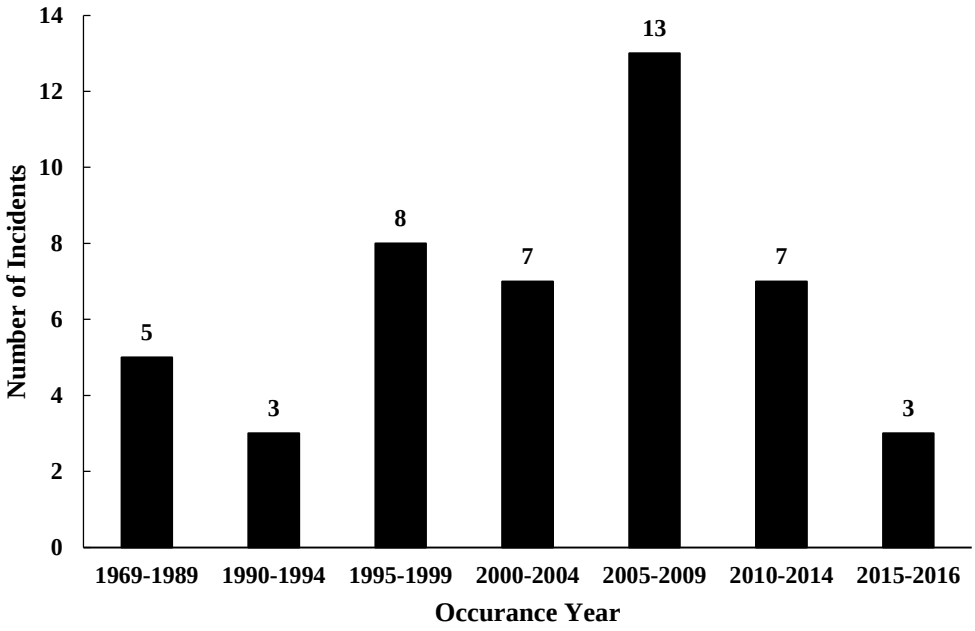

Figure 5.4: Number of health damage incidents of falsified medicine by Year (n=46).

3 cases were not included as there was no mentioning of occurrence year.

5.3.4. Nature of drug falsification

The identified incidents involved many kinds of falsified drug products. Some did not contain any active ingredient (meningitis vaccine containing no active ingredient or just salt water), or included the active ingredient in harmful amounts (traditional anti-diabetic medicine containing six times the normal dose of glibenclamide). Others involved a completely different active ingredient or incorrect formulation, or contained unacceptably high levels of impurities (cyanide-laced paracetamol or zolpidem and acetaminophen laced with metal).

Looking at the health damage caused by falsified drugs at Table 5.1, the most common category (10 cases) covered antipyretic, analgesics, (acetaminophen, paracetamol) antitussive medication (cough syrup, paracetamol, dextromethorphan), and in 8 of them, diethylene glycol was present as a contaminant (either deliberate or accidental) in the drug. Mass poisoning incidents with diethylene glycol have occurred in a number of countries over a long period.

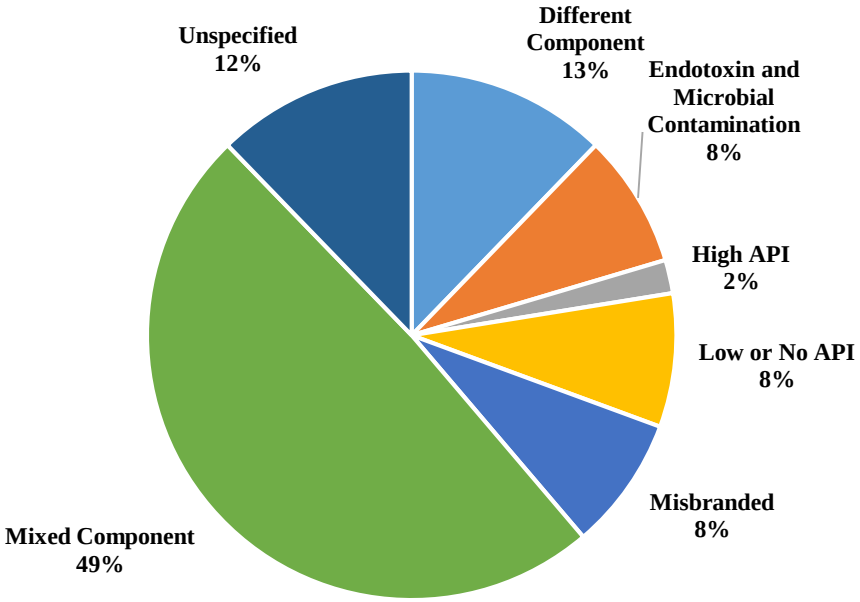

Figure 5.5: Characteristics of falsified drugs causing health damage (n=49)

Medicines containing an incorrect amount of API or a totally different kind of API appeared in at least 12 cases. Another common finding was endotoxin and microbial contamination of ophthalmic products or infusions. Fig 5.5 summarizes the types of falsified medicines associated with health damage in the incidents listed in Table 5.1.

Box 6: Potential consequences of drug falsification

- Falsified medications are associated with both direct and indirect risks to health.
- Direct risks include unknown pharmaceutically active ingredient(s) and/or impurities that may lead to serious adverse effects, dosage variability or mislabeling potentially leading to overdose, and incorrect product descriptions creating a risk for drug-drug interactions.
- Indirect risks include lack of appropriate information, lack of advice and/or management of healthcare concerns; difficulty of managing adverse effects caused by an unknown product; and unnecessary dosing changes or unwarranted dismissal of genuine therapies because of perceived lack of effect caused by variable potency of falsified products.

5.3.5. Prospects for the fight against drug falsification

A better understanding of falsified drug-related injuries and diseases, together with knowledge of the main targets of falsification are needed to develop better prevention strategies. To address this issue, better collaboration among concerned communities, including government organizations, health workers, industry and civil society, will be

essential. Especially, communication between the healthcare professional and patients needs to be improved to inform and educate patients about the risks of falsified drugs. Public awareness concerning the potential problems of internet pharmacies and other online purchasing sites also needs to be raised. Management systems for the supply chain should be improved and the secondary drug market should be better regulated. Finally, post-marketing surveillance and pharmacovigilance should be strengthened to ensure drug safety and patient safety.

5.3.6. Limitations of the study

This study has several limitations. Firstly, it covers only English language articles in the PubMed database. Also, in some of the reported cases, there was no information about specific drug involvement, exact number of patients harmed, year of occurrence or the location of the incident. In particular, several incidents that were claimed to involve hundreds of thousands of people were very poorly described. It should also be borne in mind that the results might be biased by differences in the effectiveness of reporting systems among countries; for example, less serious incidents in under-developed countries might not have been reported. In addition, different reports sometimes gave conflicting information about the same incident. Thus, we cannot estimate the true extent of the problem. Nevertheless, we believe this study of reported drug falsification incidents involving health damage will be useful to illustrate the nature and scale of the problem, and to provide a basis for further surveys in the future.

5.4. Conclusion

It is clear from the results of this study that falsified medicines impact both directly and indirectly on global public health. A wide range of medicines has been falsified in a variety of ways, and our findings may be helpful to identify particular causes for concern, such as deliberate or accidental contamination with ethylene glycol. Recognition of the problem, coordination of responses, and active engagement of key stakeholders will be essential in combating transnational pharmaceutical crime, and reducing the human cost of falsified medicines.

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Chapter 6

General conclusion and future directions

6.1. Conclusion

This research addresses several key issues that may influence future trends in the prevalence of substandard pharmaceuticals in South Asian countries. In today's context of globalization of pharmaceutical production and distribution, the findings of this study highlight the urgency of implementing continuous and ongoing monitoring of the quality of drugs as a basis for designing and implementing appropriate countermeasure to prevent the manufacture and distribution of both substandard and falsified medicines in this region. The inadequacy of the current regulatory requirements and systems in resource-poor settings provides unscrupulous manufacturers with the opportunity to sell poor quality medicines with little risk of being sanctioned. This situation is exacerbated by the current high demand for lifestyle medicines, favoring the interests of manufactures with poor technical capacity or with poor ethics, but certainly not serving the interests of the importing countries or the patients (Ravinetto et al., 2012).

Regarding the authenticity of the medicines and the legitimacy of the manufacturer and distributors, we could not clearly establish the facts, because we received little response to our enquiries from either side, as has been the case in previous studies. Nevertheless, the production of substandard medicines appears to be a vast and underreported problem, which particularly affects poorer countries. Often, investigators have found that pharmaceutical companies and governments are reluctant to respond to requests to confirm the authenticity of the product or the legitimacy of the manufacturers and distributors (Khan et al., 2009; Khan et al., 2010; Khan et al., 2012; Yoshida et al., 2014; Rahman et al., 2017). In the case of manufacturers, one of the reason may be that publicity would harm the sales of brand name products in a fiercely competitive business. We suggest that this situation is not in the long-term interests of the legitimate

pharmaceutical industry. We urge a change to mandatory reporting to governmental authorities, which should also have a legal duty to investigate, provide appropriate information, and share information across borders. This is not a role for the pharmaceutical industry, which appears to have a serious conflict of interest.

Box 7: Significance of the study

This work is the only recent survey of the quality of delayed-release omeprazole capsules and pioglitazone tablets collected in Cambodia, Myanmar, and China, or purchased via the internet for personal use. Significant proportions of these medicines were substandard, especially in the cases of samples from Myanmar and internet sources. Nevertheless, comparison of these findings with earlier surveys (Khan et al., 2012; Yoshida et al., 2014) indicates that the situation in these countries has improved in the last few years. Our findings provide a basis for recommendations and regulatory actions to further improve the situation in those countries.

Moreover, the internet, has now become the source of health-related information for millions of people (FDA, 2017; Fernandez et al., 2008). Many online sites are selling medicines for personal use, particularly omeprazole and pioglitazone, without restriction or approval. It is clear that the internet is having a great impact (Orizio et al., 2009; Siva, 2009). More than half of the sites that we found did not declare their physical location, and a majority of sites did not ask for a medical prescription in order to purchase drugs. Avoidance of prescription boundaries can be a potential disruptor at multiple levels, both at the individual level, between doctor and patient, where it represents an easy way to overcome the health professional filter in order to access drugs, and at a public health

level, where national health services can be affected by patients bypassing regulated systems. Indeed, there have been reports of concern regarding drugs storage, shipping conditions, and fraudulent and dangerous practices associated with online purchase of medicines (Weiss, 2006).

It should be noted that this thesis has focused on the situation of only two drugs, omeprazole and pioglitazone, in several Southeast Asian countries, due to limitations of time and resources. Our work does not imply that the issue of substandard medicines and variability in drug quality is of equal importance in all countries. Indeed, the problem may be more profound in low and middle income countries, for example, Cambodia and Myanmar, due to limited regulatory capacity and the high proportion of imported medicines. Nevertheless, despite limited resources, it will be very important for these countries to develop strategies for improving procurement of medicines, as well as involving stakeholders in evaluating the quality of medicines and making patients more aware of the possible consequences of taking poor quality medicines.

6.2. Policy implications and future directions

A number of important ideas and potential policy implications can be extracted from this report. Rather than picking a single framework, we consider that three broad policy goals need to be addressed – (1) increasing the national and international emphasis on substandard medicines, in addition to falsified medicines; (2) improving collaboration between medicinal regulatory authorities and manufacturers to undertake comprehensive, independent market surveillance in order to establish scale and scope of the problem, and (3) strengthening systems across the medical supply chain to improve overall supply chain management. There is also a need to undertake further research into the role of

information asymmetries in pharmaceutical supply chains, and its effect on the perceptions and actions of health professionals, consumers and patients. These studies should be performed in a manner that supports accurate cross-comparisons, and the results should be made available to the public. Pharmaceutical companies can also assist by becoming more transparent with their data on this public health challenge, as well as alerting the public promptly to potential cases of poor quality medicines. As more and more middle-income countries are emerging as important sources of pharmaceutical ingredients and finished medicinal products, there is an increasing need for comprehensive and harmonized strategies to address variability in drug quality.

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LIST OF APPENDICES

Appendix 1: Sampling form

Sampling Form | Serial No. ☐ — ☐☐☐ ☐☐ / 9or10/2014

Combating Counterfeit Medicine in Myanmar: 2014 | Code : /MM14/

PRODUCT INFORMATION

Contents	Answer	Unknown	Information Source: Label	Information Source: Verbal
Trade name of the product				
Name of active ingredients				
Strength per unit dose	g / mg as			
Salt form				
Dose form of products	☐Tablets ☐Capsules ☐Ampules ☐Others :_____			
The product is	☐ Domestically produced ☐ Imported			
Sample Classification	☐ ① 1st (A) 〈selected companies〉 ☐ ② 1st (B) 〈Loose sample〉 ☐ ③ random sampling			
Any commnets about Loose sample				
Manufacture	Name			
	Address			
Wholesaler	Name			
	Address			
Batch/Lot number				
Manufactury date	DD _____ / MM _____ / YY _____			
Expiry date	DD _____ / MM _____ / YY _____			
Registration number	☐ Yes ⇒ _____ ☐ No			
Package insert	☐ Yes ⇒ ☐Burmese ☐English ☐French ☐Others: ☐ No			
Price per Unit				
Quantity collected				

OUTLET INFORMATION

Contents	Answer	
Category of the outlet	☐ Hospital Pharmacy ☐Community Pharmacy ☐ Wholesaler ☐Others_____	
No. of Pharmacist		
No. of Pharmacy Assistant		
No. of other staff		
Name of the outlet		
Does the shop have air conditioner ?	☐ Yes ☐ No	
Are there any loose medicines?	☐ Yes ☐ No	
For Loose medicine, the container is	☐the original one supplied during the procurement ☐changed later on in the drug store	☐Unknown Information Source ☐Label ☐Verbal
How many units of this medicine does the outlet sell ?	_____ units per _____ . (e.g. month, year)	

Outlet address	Any comments ? (e.g. Is the medicine kept in a refrigerator ?)	Signature

Appendix 2: FIP checklist for the observation of samples

Tool for Visual Inspection of Medicines			
	Yes	No	Other Observations
1. PACKAGING			
1.1 Container and Closure			
Does the container and closure protect the product from the outside environment; e.g. is the container properly sealed?			
Do they assure that the product will meet the proper specifications throughout its shelf life?			
Are the container and the closure appropriate for the product inside?			
Is the container safely sealed?			
1.2 Label			
If there is a carton protecting the container, does the label on the carton match the label on the container?			
Is all information on the label legible and indelble?			
1.2.1 The trade (brand) name			
Is the trade name spelled correctly?			
Is the medicinal product (trade name) registered in the country by the Drug Regulatory Authority) ? Is the product legally sold in the coutry?			
Does the symbol ® follow the trade name?			
For blister or foil strip packed products, is the trade name indelibly impressed or imprinted onto the strip?			
1.2.2 The Active ingredient name (scientific name/generic name)			
Is the active ingredient name spelt correctly?			
Do the trade name and the active ingredient names correspond to the registered product?			

1.2.3 The manufacturer's name and logo			
Are the manufacturer's name and logo legible and correct?			
Does the logo or hologram (if applicable) look authentic?			
Does the logo or hologram (if applicable) change colour when viewed from different angles?			
1.2.4 The manufacturer's full address			
Is the manufacturer's full address legible and correct?			
Has this company or its agent registered the product in the country?			
1.2.5 The medicine strength (mg/unit)			
Is the strength - the amount of active ingredient per unit - clearly stated on the label?			
For blister or foil strip packed products, is the medicine strength indelibly impressed or imprinted onto the strip?			
1.2.6 The dosage form (e.g., tablet/capsule)			
Is the dosage form clearly indicated on the container label?			
Does the dosage form stated on the label match the actual dosage form of the medication?			
Is the indicated madicine under this dosage form registered and authorised for sale in the country?			
1.2.7 The number of units per container			
Does the number of dosage units listed on the label match the number of dosage units stated on the container?			
1.2.8 Dosage statement (if appropriate)			
Is the dosage clearly indicated on the label?			
Is the dosage stated on the label appropriate for			

the madicine in this form and strength?			
Is the product registered and authorised for sale in the country with this dosage?			
1.2.9 The batch (or lot) number			
Does the numbering system on the package correspond to that of the producting company?			
For blister or foil strip packed medicines, is the batch number indelibly impressed or imprinted onto the strip?			
1.2.10 The date of manufacture and the expiry date			
Are the manufacture and expiry dates clearly indicated on the label?			
For blister or foil strip packed products, is the expiry date indelibly impressed or imprinted onto the strip?			
1.2.11 Storage information			
Are the storage conditions indicated on the label?			
Has the product been properly stored?			
1.3 Leaflet or package insert			
Is the package insert printed on the same coloured or same quality paper as the original (If available to compare) or does it look familiar?			
Is the ink on the package insert or packaging smudge-proof?			
Does the informationb on the package insert match the information on the product container?			
2. PHYSICAL CHARACTERISTICS OF TABLETS/CAPSULES			
2.1 Uniformity of Shape			
Are the tablets/capsules uniform in shape?			
2.2 Uniformity of Size			
Are the tablets/capsules uniform in size?			
2.3 Uniformity of Colour			

Are the tablets/capsules uniform in colour?			
2.4 Uniformity of Texture			
Do the tablats have a uniform coating?			
Is the base of the tablets fully covered?			
Are the tablets unifomly polished, free of powder, and non-sticking?			
2.5 Markings (scoring, letters, etc)			
Are markings uniform and identical?			
Does the logo (if present) match that of the manufacturing company?			
2.6 Breaks, Cracks and Splits			
Are the tablets/capsules free of breaks, cracks, splits or pinholes?			
2.7 Embedded surface spots or contamination			
Are the tablets/capsules free of embedded surface spots and foreign particle contamination?			
2.8 Presence of empty capsules in the case of asample of capsules			
Is the sample examined free of empty capsules?			
2.9 Smell			
Does the medicine smell the same as the original (If available)? Does it smell peculiar?			

Appendix 3-1: First contact e-mail format to manufacturer for authenticity investigation

To whom it may concern,

Date-

Greeting from Japan.

To improve pharmaceutical situation and access of quality medicines in Myanmar the Department of Drug Management and Policy, Kanazawa University, Japan is collaborating with the Food and Drug Administration, Myanmar on the Project on Counterfeit Programs in Myanmar in 2014. This project is being supported by the Japan Pharmaceutical Manufacturers Association (JPMA).

As a part of the activities of the project's, in 2014, a few samples of medicines originated from various countries were collected from the pharmaceutical markets of Myanmar. At this moment, we are verifying all the samples with concerned medicine regulatory authorities and the manufacturers supposed to have produced them. In this regard, cooperation of manufacturers is essential to verify the samples. Among the collected samples, we have "**Sample Name**", supposed to be manufactured by **Manufacturer Name**.

We have attached here a questionnaire with photos of the samples. It would be much appreciated if you kindly send us back your filled out questionnaire at your earliest convenience, preferably by '**Date**'.

Additionally, we would like to send you a part of the physical sample to check. Please let us know your convenient address to receive the samples.

In case you are not the right person in your company to deal with this request, I would appreciate if you kindly forward this e-mail to someone who can handle this request.

Thank you in advance for your kind cooperation. We are looking forward to hearing from you.

Sincerely yours,

Mohammad Sofiqur Rahman
For Kazuko KIMURA, Prof., PhD,
Department of Drug Management and Policy,
Institute of Medical, Pharmaceutical and Health Sciences,
Kanazawa University
Kakuma-machi, Kanazawa-city, Ishikawa, Japan 920-1192
http://www.p.kanazawa-u.ac.jp/e/lab/kokusai.html
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E-mail: kimurak@p.kanazawa-u.ac.jp

Appendix 3-2: Reminder e-mail format to manufacturer for authenticity investigation

Reminder for Authentication of **'Brand Name'**

Dear Sir or Madam,

Warm greetings from Japan. This is Mohammad Sofiqur Rahman from Kanazawa University.

We have contacted you by e-mail on '**Date**' regarding the Myanmar 2014 project of combating counterfeit medicines in Myanmar.

As of writing this e-mail, it seems that we have not received any relevant response from you yet. I'd appreciate if you could send us the filled questionnaire immediately.

If there is any question or inconvenience, please kindly inform us.

Thank you in advance for your kind cooperation. We are looking forward to hearing from you soon.

Sincerely yours,

Mohammad Sofiqur Rahman
Department of Drug Management and Policy,
Institute of Medical, Pharmaceutical and Health Sciences,
Kanazawa University
Kakuma-machi, Kanazawa-city, Ishikawa, Japan 920-1192
http://www.p.kanazawa-u.ac.jp/e/lab/kokusai.html
E-mail: dmpc14@p.kanazawa-u.ac.jp
Tel.: +81 76 234 4402 Fax: +81 76 264 6286

Appendix 4: Questionnaire format for manufacturer for authenticity investigation of samples

KANAZAWA University
Institute of Medical, Pharmaceutical and Health Sciences

QUESTIONNAIRE FOR AUTHENTICITY INVESTIGATION

MANUFACTURER: X

Scope: The purpose of this questionnaire is to authenticate a medicinal sample/s collected in conjunction with the anti-counterfeit initiatives of the Food and Drug Administration, Myanmar

Instructions:

- Please refer to the attached sample(s) or photos and check appropriate boxes ☑ for your answer.
- Please provide detailed information whenever it is required.

REGISTRATION			
1	Do you have a License Number in the manufacturing country issued by the Medicine Regulatory Authority? ☐Yes/ Detailed number: _____ ☐No		
2	Are you certified on Good Manufacturing Practices?	☐Yes	☐No
3	If certified, please detail the name of certifying authority.		
PACKAGING AND MARKETING			
4	Are these packages/containers of the samples made by your company originally?	☐Yes	☐No
5	If you checked 'No' for the above question, please let us know who prepare the package: ☐distributor ☐other company;_____ ☐unknown		
6	During shipment to importing country/Myanmar, do you transport your medicines separately from their packages/containers?	☐Yes	☐No

CONTACT INFORMATION	
Responded by–	Date: / /
Name:	
Professional affiliation/position:	
Company full address:	
Tel / Fax:	E-mail:

KANAZAWA University
Institute of Medical, Pharmaceutical and Health Sciences

SAMPLE CODE:

SAMPLE AUTHENTICATION				
	Sample's description		Pl. check appropriate box, if the information provided is identical to your genuine sample	
1	Trade Name		☐Yes	☐No
2	Active Ingredient & Strength		☐Yes	☐No
3	Dosage Form		☐Yes	☐No
4	Manufacturer's Name		☐Yes	☐No
5	Manufacturer's Address		☐Yes	☐No
6	Batch/Lot Number:		☐Yes	☐No
7	Manufacturing Date:		☐Yes	☐No
8	Expiry Date:		☐Yes	☐No
9	Distributor's Name		☐Yes	☐No
10	Distributor's Country		☐Yes	☐No
11	Myanmar Registration No.		☐Yes	☐No
12	Manufacturing License Number		☐Yes	☐No
13	Is the logo authentic?		☐Yes	☐No
14	Is the trade name written appropriately (font, spell, ®)?	font	☐Yes	☐No
		spell	☐Yes	☐No
		®	☐Yes	☐No
15	Are the active ingredient(s) name(s) written appropriately?		☐Yes	☐No
16	Does the physical characteristics of the dosage form are uniform and consistent?	form	☐Yes	☐No
		shape	☐Yes	☐No
		color	☐Yes	☐No
		coating	☐Yes	☐No
		size	☐Yes	☐No
17	Is the product under this dosage form registered and authorized for sale in Myanmar?		☐Yes	☐No
18	Please write correct information in the space provided below, if you checked 'No' to any of the above points (1-17)			
19	Is this medicine Genuine or Counterfeit?		☐Genuine	☐Counterfeit
20	If you checked 'Counterfeit' for the above question, please indicate the details about the difference of Genuine product and the Counterfeit one.			

MARKETING IN SAMPLING COUNTRY			
21	Is the sample medicine approved by the Drug Regulatory Authority in the manufacturing country? ☐Yes / Provide approval / registration number;_____ ☐No		
22	Is the sample medicine approved for marketing in Myanmar?	☐Yes	☐No
23	If you checked 'No' to the above question, please answer following two additional questions:		
	i. Please write the countries where this medicine is approved for marketing.		
	ii. Do you know that this medicine is sold in Myanmar?	☐Yes	☐No

Appendix 5: E-mail format for MRAs for authenticity investigation of manufacturer and samples

KANAZAWA UNIVERSITY
Institute of Medical, Pharmaceutical and Health Sciences

Subject: Verification of Manufacturing Approval for the Project of Counterfeit Programme in Myanmar 2014

Dear X

Greetings from Japan.

To improve the pharmaceutical situation and access of quality medicines in Myanmar, the Department of Drug Management and Policy, Kanazawa University, Japan has been collaborating with the Food and Drug Administration, Myanmar. This project is being supported by the Japan Pharmaceutical Manufacturers Association (JPMA)

As a part of the activities of the project, 2014, samples of medicines originated from various countries were collected from the pharmaceutical markets of the Myanmar. At this moment, we are verifying all the samples with concerned medicine regulatory authorities and the manufacturers supposed to have produced them. In this regard, cooperation of medicines regulatory authorities is essential to verify the legitimacy of the samples.

Among the collected samples, we have **'Product Name'** supposed to be manufactured by **'Manufacturer Name'**.

We attached here a questionnaire with the labeled information of the samples. It would be much appreciated if you kindly send us back your filled out questionnaire at your earliest convenience, preferably by '**Date**'.

In case you are not the right person in your agency to deal with this request, I would appreciate if you kindly forward this e-mail to the person who may be able to handle this request.

Thank you in advance for your kind cooperation. We are looking forward to hearing from you soon.

Sincerely yours,

Mohammad Sofiqur Rahman
Department of Drug Management and Policy,
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For
Kazuko KIMURA, Prof., PhD,
E-mail: kimurak@p.kanazawa-u.ac.jp

Appendix 6: Questionnaire format for MRAs for authenticity investigation of manufacturer and samples

KANAZAWA UNIVERSITY
Institute of Medical, Pharmaceutical and Health Sciences

MEDICINE AUTHENTICATION FORM

For Drug Regulatory Authority of Manufacturing Country

Please provide necessary information for each of the manufacturers and their medicine products mentioned below. If you have additional information that might be important to judge whether the medicine is counterfeit or not, please indicate such in the remarks column.

Name of the Manufacturer: X **Country: X**			
1. Is this manufacturer licensed by the Drug Regulatory Authority of your country?			□Yes □No
2. If Yes, please mention manufacturer's License Number:			
3. Is this a GMP qualified manufacturer of your country?			□Yes □No
Products			
Please check an appropriate box, if the regulatory authority of your country approves the manufacturer to produce mentioned medicine(s).			
Trade Name, strength, form	Active ingredient	Approval status	Remarks (if any)
		□Yes □No	

Thank you very much for your kind cooperation!

Appendix 7: E-mail format for importing country for registration verification of manufacturer and samples

Registration verification

Dr. Theingi Zin
Director (Drug)
Department of Food and Drug Administration
Ministry of Health, Myanmar

Dear Madam,
Please take my heartfelt greet from Japan. Thank you very much for your continued cooperation on the project of combating counterfeit medicine in Myanmar. As a part of our project we are doing authenticity investigation of the samples collected from Myanmar just like the previous years. In that case, we are in need to verify manufacturers and their samples of 2014 whether they are registered with your department or not. In this regard, we made an information sheet of the samples of 2014. Please find attached the questionnaire along with the photos of the samples.
It would be much appreciated if you would kindly fill out the information sheet and send us back by e-mail, fax or air mail at your earliest convenience. We are very much aware of that this request might be an extra task for your organization, but we hope that you will be kind enough and able to manage. We express our sincere appreciation in advance for your cooperation and are looking forward to hearing from you.

Sincerely yours,
Mohammad Sofiqur Rahman
Drug Management and Policy Department,
Division of Pharmaceutical Science
Institute of Medical, Pharmaceutical and Health Sciences,
Kanazawa University
Kakuma-machi, Kanazawa-city, Ishikawa, Japan 920-1192
http://www.p.kanazawa-u.ac.jp/e/lab/kokusai.html
E-mail: dmpc14@p.kanazawa-u.ac.jp
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For
Kazuko KIMURA, Prof., PhD,
E-mail: kimurak@p.kanazawa-u.ac.jp

Appendix 8: Questionnaire format for importing country for registration verification of manufacturer and samples

Registration Verification

For Department of Food And Drug Administration, Ministry of Health, Myanmar 2014

Omeprazole

Please check appropriate boxes ☑ on confirming registration of the manufacturers and their products listed below. If the registration number does not exist, please check □No in Registration column. If the registration number is old, please write down the new number against each product in Comments column. In case the registered package size is different from the registration or you have any comments, please write down in Comments column.

Manufacturer's Name	Register	Code	Brand Name /Strength (package size)	Labeled registration Number	Registration	Comments
Country Name						
Manufacturer Name	□Yes □No	Sample Code			□Yes □No	□This is old number New number_____ □Registered package size is different _____ □any comments

Appendix 9: Quantity & content uniformity test results of omeprazole collected from Myanmar in 2014

1st stage

			Kanazawa Univ. Content uniformity test (1st stage)								tolerance AV≦15.0								BP 95.0≦mean≦105	
ID	Serial No	Sample Code	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsule 3	% of Quantity Capsule 4	% of Quantity Capsule 5	% of Quantity Capsule 6	% of Quantity Capsule 7	% of Quantity Capsule 8	% of Quantity Capsule 9	% of Quantity Capsule 10	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	AV (Acceptance Value)	Judge	Mean % of Quantity	Judge
4	A-001	A001/MM14/YG.	101.2	94.0	105.6	98.6	101.9	98.5	95.0	95.6	102.6	102.7	99.6	3.8	3.9	8.2	Pass	99.6	Pass
5	A-002	A002/MM14/YG.	101.6	106.5	107.0	106.7	106.5	105.2	106.5	104.5	109.7	109.8	106.4	2.4	2.2	0.8	Pass	106.4	Fail
6	A-011	A011/MM14/YG.	100.0	93.9	99.7	95.4	96.7	97.9	98.4	90.9	104.0	103.9	98.8	3.2	3.2	7.6	Pass	98.8	Pass
7	A-012	A012/MM14/YG.	56.5	47.1	95.7	99.2	77.9	47.6	83.0	72.5	85.2	99.6	76.4	20.1	26.4	70.4	Fail	76.4	Fail
8	A-015	A015/MM14/YG.	90.0	90.9	92.3	92.2	95.9	95.4	92.5	94.4	93.4	92.2	92.9	1.9	2.0	10.1	Pass	92.9	Fail
10	A-026	A026/MM14/YG.	101.4	106.5	106.8	106.7	106.5	105.1	107.9	107.4	109.2	109.7	106.7	2.3	2.2	0.3	Pass	106.7	Fail
11	A-033	A033/MM14/YG.	75.6	84.7	81.9	86.5	101.0	80.1	99.1	100.1	95.9	91.3	89.6	9.1	10.2	30.8	Fail	89.6	Fail
12	A-034	A034/MM14/YG.	91.1	91.6	92.7	97.9	99.0	97.1	94.9	96.7	93.7	93.8	94.9	2.7	2.9	10.2	Pass	94.9	Pass
13	A-038	A038/MM14/YG.	89.8	92.1	89.0	88.8	90.8	93.0	92.2	93.5	90.0	84.7	90.4	2.6	2.9	14.3	Pass	90.4	Fail
14	A-039	A039/MM14/YG.	93.2	98.1	96.6	99.7	95.5	94.3	97.0	97.2	96.9	101.7	97.0	2.5	2.5	7.4	Pass	97.0	Pass
15	A-041	A041/MM14/YG.	109.2	107.2	107.9	106.3	102.1	105.1	104.5	105.3	106.4	100.3	105.4	2.7	2.5	2.4	Pass	105.4	Pass
16	A-042	A042/MM14/YG.	99.5	107.6	104.4	106.9	104.4	109.8	107.9	109.4	108.3	105.4	106.4	3.1	2.9	2.5	Pass	106.4	Fail
17	A-050	A050/MM14/YG.	90.1	95.5	92.5	95.0	96.7	103.7	98.3	90.8	95.4	97.0	95.5	3.9	4.1	12.4	Pass	95.5	Pass
18	A-060	A060/MM14/YG.	99.6	108.0	99.8	98.9	106.3	105.3	104.0	99.5	100.2	102.9	102.4	3.3	3.2	7.0	Pass	102.4	Pass
19	A-061	A061/MM14/YG.	92.1	102.4	99.3	96.7	92.8	98.1	95.1	100.4	98.0	98.5	97.3	3.3	3.4	9.0	Pass	97.3	Pass
20	A-065	A065/MM14/YG.	92.3	94.7	98.9	100.1	99.6	95.7	93.9	95.3	92.7	97.2	96.0	2.8	2.9	9.1	Pass	96.0	Pass
22	A-067	A067/MM14/YG.	88.1	99.5	100.1	94.7	95.0	89.9	98.0	87.3	90.8	91.6	93.5	4.7	5.0	16.2	Fail	93.5	Fail
23	A-076	A076/MM14/YG.	88.2	87.8	86.7	97.1	83.7	84.2	88.3	99.3	85.2	105.7	90.0	6.9	7.6	25.0	Fail	90.0	Fail
24	A-078	A078/MM14/YG.	99.8	94.0	62.2	62.5	76.6	45.5	73.8	90.3	76.0	78.7	75.9	16.4	21.5	61.8	Fail	75.9	Fail
25	A-084	A084/MM14/YG.	99.8	107.9	104.5	107.2	104.5	109.8	107.8	109.6	108.4	105.8	106.5	3.0	2.8	2.2	Pass	106.5	Fail
26	A-091	A091/MM14/YG.	93.3	94.5	96.5	91.2	96.4	95.7	93.8	92.6	98.3	98.7	95.1	2.4	2.6	9.3	Pass	95.1	Pass
27	A-096	A096/MM14/YG.	98.4	103.4	96.8	103.9	100.1	99.0	94.2	99.7	98.1	95.7	98.9	3.1	3.1	7.4	Pass	98.9	Pass
28	A-097	A097/MM14/YG.	94.1	103.4	99.3	101.9	96.4	104.2	97.3	103.5	98.6	104.0	100.3	3.6	3.6	8.7	Pass	100.3	Pass
29	A-101	A101/MM14/YG.	95.2	90.3	96.8	103.7	95.0	92.6	98.2	90.7	95.9	97.1	95.5	3.9	4.1	12.4	Pass	95.5	Pass
30	A-106	A106/MM14/YG.	92.5	92.6	96.1	92.2	92.3	90.0	91.1	93.6	94.5	95.4	93.0	1.9	2.0	10.0	Pass	93.0	Fail
31	A-107	A107/MM14/YG.	94.8	92.6	97.8	98.2	97.0	92.0	98.3	96.7	99.3	96.0	96.3	2.5	2.6	8.2	Pass	96.3	Pass
33	A-114	A114/MM14/YG.	97.1	93.7	96.7	97.7	94.0	93.4	94.0	96.9	91.6	93.9	94.9	2.0	2.1	8.5	Pass	94.9	Pass

			Kanazawa Univ. Content uniformity test (1st stage)							tolerance: AV≦ 15.0								BP 95.0≦ mean≦ 105	
ID	Serial No	Sample Code	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsule 3	% of Quantity Capsule 4	% of Quantity Capsule 5	% of Quantity Capsule 6	% of Quantity Capsule 7	% of Quantity Capsule 8	% of Quantity Capsule 9	% of Quantity Capsule 10	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	AV (Acceptance Value)	Judge	Mean % of Quantity	Judge
##	B-005	B-005/MM14/YC	99.1	108.0	100.1	99.8	99.6	106.5	103.0	100.4	104.1	107.9	102.9	3.6	3.5	7.2	Pass	102.9	Pass
##	B-006	B-006/MM14/YC	96.4	94.7	95.8	91.6	97.6	92.5	97.6	96.6	98.5	98.0	95.9	2.3	2.4	8.2	Pass	95.9	Pass
##	B-007	B-007/MM14/YC	89.8	92.1	89.1	88.9	91.0	93.0	92.3	93.5	89.9	84.8	90.4	2.6	2.9	14.2	Pass	90.4	Fail
##	B-008	B-008/MM14/YC	102.0	95.8	110.0	107.2	107.8	108.5	106.7	98.2	105.6	105.3	104.7	4.6	4.4	7.9	Pass	104.7	Pass
##	B-011	B-011/MM14/YC	102.7	102.6	105.7	101.5	96.8	106.0	106.1	105.5	101.0	106.7	103.5	3.1	3.0	5.6	Pass	103.5	Pass
##	B-013	B-013/MM14/YC	90.7	95.5	93.6	91.0	99.3	90.8	96.0	91.3	98.0	91.7	93.8	3.2	3.4	12.4	Pass	93.8	Fail
##	B-015	B-015/MM14/YC	98.6	113.1	90.3	98.3	116.2	96.6	100.7	108.9	113.3	113.5	104.9	9.1	8.6	18.3	Fail	104.9	Pass
##	B-017	B-017/MM14/YC	89.0	91.5	96.7	95.8	98.8	100.1	88.1	90.3	93.3	92.7	93.6	4.1	4.4	14.7	Pass	93.6	Fail
##	B-036	B-036/MM14/YC	96.2	97.8	99.7	95.8	98.9	94.6	93.0	93.6	98.6	90.6	95.9	2.9	3.1	9.7	Pass	95.9	Pass
##	B-037	B-037/MM14/YC	92.4	93.0	94.0	99.5	100.6	98.6	96.3	98.2	94.8	95.2	96.3	2.8	3.0	9.1	Pass	96.3	Pass
##	B-045	B-045/MM14/YC	93.0	78.3	77.4	76.2	89.1	94.1	91.4	97.8	82.9	87.6	86.8	7.7	8.8	30.1	Fail	86.8	Fail
##	B-049	B-049/MM14/YC	80.6	69.2	77.8	80.0	89.5	78.4	85.0	85.6	82.6	83.4	81.2	5.5	6.8	30.5	Fail	81.2	Fail
##	B-054	B-054/MM14/YC	93.5	94.2	102.0	93.3	96.1	93.1	98.5	100.9	92.9	93.8	95.8	3.4	3.6	10.9	Pass	95.8	Pass
##	B-059	B-059/MM14/YC	98.3	90.0	97.8	90.3	99.0	101.3	101.6	104.2	103.4	103.3	98.9	5.1	5.2	12.2	Pass	98.9	Pass
##	B-065	B-065/MM14/YC	90.5	91.9	91.6	95.1	95.2	96.6	91.0	90.8	91.1	96.5	93.0	2.5	2.7	11.5	Pass	93.0	Fail
##	B-070	B-070/MM14/YC	95.9	94.0	97.5	91.8	91.4	90.8	99.0	100.9	96.1	104.8	96.2	4.5	4.7	13.0	Pass	96.2	Pass
##	B-077	B-077/MM14/YC	86.1	91.8	87.7	83.8	90.4	86.5	88.2	89.4	84.2	90.7	87.9	2.7	3.1	17.2	Fail	87.9	Fail
##	B-090	B-090/MM14/YC	97.1	94.1	95.2	100.0	99.5	100.9	92.6	105.0	97.8	102.7	98.5	3.9	4.0	9.4	Pass	98.5	Pass
##	B-092	B-092/MM14/YC	99.9	103.1	98.4	102.9	105.9	94.3	102.8	101.5	98.1	103.8	101.1	3.4	3.4	8.2	Pass	101.1	Pass
##	B-098	B-098/MM14/YC	97.5	95.4	81.2	90.8	100.2	98.4	100.1	94.5	93.9	101.2	95.3	6.0	6.2	17.5	Fail	95.3	Pass
##	B-106	B106/MM14/YG.	98.9	93.0	95.9	96.4	100.3	99.5	92.0	96.3	100.5	103.6	97.6	3.6	3.7	9.5	Pass	97.6	Pass
##	B-108	B108/MM14/YG.	101.2	101.4	98.2	99.3	96.9	96.9	98.6	96.0	99.1	101.5	98.9	2.0	2.0	4.7	Pass	98.9	Pass
##	B-110	B110/MM14/YG.	87.9	89.2	89.3	87.9	90.6	87.9	88.6	85.5	91.0	93.8	89.2	2.2	2.5	5.4	Pass	89.2	Fail
2	PA-005	PA005/MM14/YC	96.3	101.6	92.5	98.5	99.4	96.6	97.9	96.6	100.0	98.2	97.8	2.5	2.5	6.7	Pass	97.8	Pass
3	PA-006	PA006/MM14/YC	107.7	105.9	104.9	101.8	99.9	104.6	103.2	104.3	107.8	105.1	104.5	2.4	2.3	2.8	Pass	104.5	Pass
##	PB-002	PB-002/MM14/^	90.9	81.7	99.9	92.7	93.5	85.0	85.6	87.3	85.5	86.5	88.8	5.4	6.0	22.5	Fail	88.8	Fail
##	PB-003	PB-003/MM14/^	92.1	96.0	90.3	91.2	92.0	95.0	94.2	93.6	95.9	96.5	93.7	2.2	2.3	10.1	Pass	93.7	Fail

			Kanazawa Univ. Content uniformity test (1st stage)							tolerance: AV≦ 15.0								BP 95.0≦ mean≦ 105	
ID	Serial No	Sample Code	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsule 3	% of Quantity Capsule 4	% of Quantity Capsule 5	% of Quantity Capsule 6	% of Quantity Capsule 7	% of Quantity Capsule 8	% of Quantity Capsule 9	% of Quantity Capsule 10	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	AV (Acceptance Value)	Judge	Mean % of Quantity	Judge
			Kanazawa Univ. Content uniformity test (1st stage)							tolerance: AV≦ 15.0								USP 90.0≦ mean≦ 110	
##	B-016	B-016/MM14/YC	106.7	105.7	103.3	107.9	105.9	97.6	104.6	94.6	103.2	104.0	103.4	4.1	4.0	8.1	Pass	103.4	Pass
32	A-113	A113/MM14/YG.	93.4	106.4	98.1	93.7	103.5	94.4	91.0	95.3	94.7	105.6	97.6	5.5	5.7	14.2	Pass	97.6	Pass
##	B-074	B-074/MM14/YC	88.9	63.0	70.3	62.4	86.7	84.7	70.0	70.9	95.3	91.9	78.4	12.3	15.7	49.7	Fail	78.4	Fail
9	A-021	A021/MM14/YG.	93.7	98.7	97.3	93.1	102.3	101.1	92.4	93.3	90.7	107.7	97.0	5.4	5.6	14.4	Pass	97.0	Pass
21	A-066	A066/MM14/YG.	100.0	94.7	101.4	102.5	107.7	92.1	98.3	103.3	103.3	95.2	99.9	4.8	4.8	11.5	Pass	99.9	Pass
##	B-012	B-012/MM14/YC	102.2	96.2	110.0	107.4	107.9	108.5	106.8	98.5	103.9	105.3	104.7	4.5	4.3	7.7	Pass	104.7	Pass
##	B-043	B-043/MM14/YC	105.1	104.8	106.7	104.0	108.5	103.9	108.2	107.7	105.3	105.7	106.0	1.7	1.6	9.3	Pass	106.0	Pass
##	B-046	B-046/MM14/YC	109.7	108.2	109.3	100.4	108.1	109.8	106.6	102.4	107.7	107.6	107.0	3.2	2.9	2.1	Pass	107.0	Pass
##	B-071	B-071/MM14/YC	98.0	92.7	99.3	100.4	105.5	90.2	96.2	101.2	101.2	93.3	97.8	4.7	4.8	11.9	Pass	97.8	Pass
##	B-078	B-078/MM14/YC	97.1	93.1	100.6	106.6	99.6	98.8	93.2	98.1	104.6	93.3	98.5	4.7	4.7	11.2	Pass	98.5	Pass
1	PA-004	PA004/MM14/YC	90.1	104.8	101.3	101.7	97.1	108.1	100.5	102.6	99.5	103.5	100.9	4.8	4.8	11.6	Pass	100.9	Pass

Appendix 10: Quantity & content uniformity test results of omeprazole collected from Myanmar in 2014

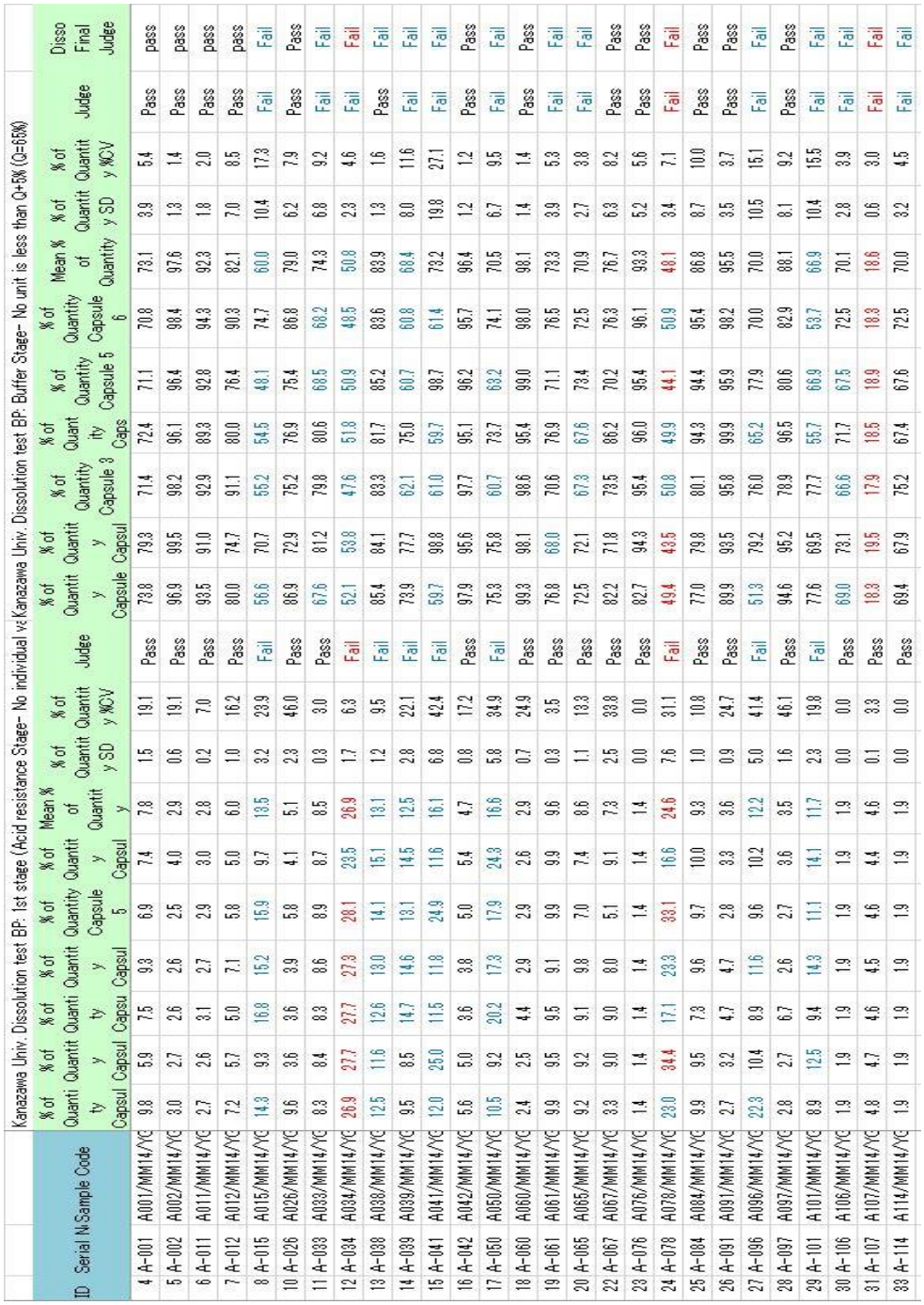
2nd stage

			Kanazawa Univ. Content uniformity test (2nd stage)												nd no individual content is less than 0.75M or more than 1.25M														95.0≦mean≦105	
ID	Serial No	Sample Code	% of Quantity Capsul	% of Quantity Capsu	% of Quantity Capsul	% of Quantity Capsul	% of Quantity Capsul	% of Quantity Capsu	% of Quantity Capsul	% of Quantity Capsul	% of Quantity Caps	% of Quantity Caps	% of Quantity Cap	% of Quantity Capsu	% of Quantity Capsul	% of Quantity Capsu	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Cap	% of Quantity Capsu	% of Quantity Caps	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	M value for AV	AV (Acceptance)	Judge	Kanazawa Univ. Quantity test	Judge
4	A-001	A001/MM14/YG																									8.2	Pass	99.6	Pass
5	A-002	A002/MM14/YG																									0.8	Pass	106.4	Fail
6	A-011	A011/MM14/YG																									7.6	Pass	98.8	Pass
7	A-012	A012/MM14/YG																									70.4	Fail	76.4	Fail
8	A-015	A015/MM14/YG																									10.1	Pass	92.9	Fail
10	A-026	A026/MM14/YG																									0.3	Pass	106.7	Fail
11	A-033	A033/MM14/YG	109.2	95.3	93.1	91.4	97.5	98.6	109.9	98.7	94.3	89.2	92.7	103.1	95.8	90.7	90.1	88.0	99.3	88.9	85.3	96.8	93.5	7.9	8.4	98.5	20.8	Fail	89.6	Fail
12	A-034	A034/MM14/YG																									10.2	Pass	94.9	Pass
13	A-038	A038/MM14/YG																									14.3	Pass	90.4	Fail
14	A-039	A039/MM14/YG																									7.4	Pass	97.0	Pass
15	A-041	A041/MM14/YG																									2.4	Pass	105.4	Pass
16	A-042	A042/MM14/YG																									2.5	Pass	106.4	Fail
17	A-050	A050/MM14/YG																									12.4	Pass	95.5	Pass
18	A-060	A060/MM14/YG																									7.0	Pass	102.4	Pass
19	A-061	A061/MM14/YG																									9.0	Pass	97.3	Pass
20	A-065	A065/MM14/YG																									9.1	Pass	96.0	Pass
22	A-067	A067/MM14/YG	90.3	96.0	102.0	98.0	101.1	93.0	92.4	101.6	104.0	95.1	98.0	103.5	93.5	96.2	97.9	87.3	88.3	92.0	97.4	87.7	95.0	5.0	5.3	98.5	13.6	Pass	93.5	Fail
23	A-076	A076/MM14/YG	88.9	85.0	89.7	87.8	102.7	97.3	98.9	109.5	97.1	90.5	92.6	92.9	88.6	95.2	98.7	108.9	96.7	81.7	95.7	95.7	93.2	7.3	7.8	98.5	19.9	Fail	90.0	Fail
24	A-078	A078/MM14/YG																									61.8	Fail	75.9	Fail
25	A-084	A084/MM14/YG																									2.2	Pass	106.5	Fail
26	A-091	A091/MM14/YG																									9.3	Pass	95.1	Pass
27	A-096	A096/MM14/YG																									7.4	Pass	98.9	Pass
28	A-097	A097/MM14/YG																									8.7	Pass	100.3	Pass
29	A-101	A101/MM14/YG																									12.4	Pass	95.5	Pass
30	A-106	A106/MM14/YG																									10.0	Pass	93.0	Fail
31	A-107	A107/MM14/YG																									8.2	Pass	96.3	Pass
33	A-114	A114/MM14/YG																									8.5	Pass	94.9	Pass

ID	Serial N	Sample Code	% of Quanti ty Capsul	% of Quanti ty Capsu	% of Quanti ty Capsul	% of Quantit y Capsul	% of Quantit y Capsul	% of Quanti ty Capsu	% of Quantit y Capsul	% of Quantit y Capsul	% of Quan tity Caps	% of Quant ity Caps	% of Qua ntity Cap	% of Quant ity Capsu	% of Quanti ty Capsul	% of Quanti ty Capsu	% of Quan tity Caps	% of Quant ity Caps	% of Quan tity Caps	% of Qua ntity Cap	% of Quanti ty Capsu	% of Quant ity Caps	Mean % of Quanti ty	% of Quanti ty SD	% of Quan tity %CV	M value for AV	AV (Acc eptan ce	Judge	Kanazaw a Univ. Quantity test	Judge
			Kanazawa Univ. Content uniformity test (2nd stage)														nd no individual content is less than 0.75M or more than 1.25I												95.0≦mean≦105	
##	B-005	B-005/MM14/Y																									7.2	Pass	102.9	Pass
##	B-006	B-006/MM14/Y																									8.2	Pass	95.9	Pass
##	B-007	B-007/MM14/Y																									14.2	Pass	90.4	Fail
##	B-008	B-008/MM14/Y																									7.9	Pass	104.7	Pass
##	B-011	B-011/MM14/Y																									5.6	Pass	103.5	Pass
##	B-013	B-013/MM14/Y																									12.4	Pass	93.8	Fail
##	B-015	B-015/MM14/Y	106.1	96.1	109.7	111.1	98.0	101.1	106.5	92.3	97.5	108.2	####	108.5	108.7	107.6	107.5	98.5	110.9	99.6	108.6	107.2	104.7	6.8	6.5	101.5	10.4	Pass	104.9	Pass
##	B-017	B-017/MM14/Y																									14.7	Pass	93.6	Fail
##	B-036	B-036/MM14/Y																									9.7	Pass	95.9	Pass
##	B-037	B-037/MM14/Y																									9.1	Pass	96.3	Pass
##	B-045	B-045/MM14/Y	79.9	91.1	90.9	95.6	95.4	104.3	102.6	104.3	87.3	91.6	91.8	93.4	96.9	89.8	93.8	94.0	85.5	95.2	95.5	97.6	91.5	7.3	7.9	98.5	21.6	Fail	86.8	Fail
##	B-049	B-049/MM14/Y																									30.5	Fail	81.2	Fail
##	B-054	B-054/MM14/Y																									10.9	Pass	95.8	Pass
##	B-059	B-059/MM14/Y																									12.2	Pass	98.9	Pass
##	B-065	B-065/MM14/Y																									11.5	Pass	93.0	Fail
##	B-070	B-070/MM14/Y																									13.0	Pass	96.2	Pass
##	B-077	B-077/MM14/Y	90.0	90.2	87.1	93.9	90.6	92.2	92.3	94.5	92.4	93.0	93.9	94.0	90.7	95.6	91.5	94.3	92.0	93.7	92.7	93.5	90.9	3.1	3.4	98.5	13.8	Pass	87.9	Fail
##	B-090	B-090/MM14/Y																									9.4	Pass	98.5	Pass
##	B-092	B-092/MM14/Y																									8.2	Pass	101.1	Pass
##	B-098	B-098/MM14/Y	93.5	95.1	88.7	96.6	92.9	97.0	86.8	95.2	91.9	95.9	82.5	91.6	78.9	90.9	90.8	90.0	85.7	84.2	90.6	82.8	91.8	5.9	6.4	98.5	18.4	Fail	95.3	Pass
##	B-106	B106/MM14/YC																									9.5	Pass	97.6	Pass
##	B-108	B108/MM14/YC																									4.7	Pass	98.9	Pass
##	B-110	B110/MM14/YC	91.7	93.0	94.2	91.0	93.6	92.6	94.1	92.6	95.9	94.6	93.7	96.0	90.5	87.4	90.9	94.8	94.4	90.0	90.6	92.2	91.5	2.7	3.0	98.5	12.5	Pass	89.2	Fail
2	PA-005	PA005/MM14/Y																									6.7	Pass	97.8	Pass
3	PA-006	PA006/MM14/Y																									2.8	Pass	104.5	Pass
##	PB-002	PB-002/MM14/	98.8	102.9	93.9	89.2	88.4	92.5	93.6	100.4	90.5	96.6	####	94.0	95.9	100.6	98.1	92.9	104.4	92.8	96.9	100.1	93.8	6.0	6.4	98.5	16.7	Fail	88.8	Fail
##	PB-003	PB-003/MM14/																									10.1	Pass	93.7	Fail
			Kanazawa Univ. Content uniformity test (2nd stage)														nd no individual content is less than 0.75M or more than 1.25I												95.0≦mean≦105	
ID	Serial N	Sample Code	% of Quanti ty Capsul	% of Quanti ty Capsu	% of Quanti ty Capsul	% of Quantit y Capsul	% of Quantit y Capsul	% of Quanti ty Capsu	% of Quantit y Capsul	% of Quantit y Capsul	% of Quan tity Caps	% of Quant ity Caps	% of Qua ntity Cap	% of Quant ity Capsu	% of Quanti ty Capsul	% of Quanti ty Capsu	% of Quan tity Caps	% of Quant ity Caps	% of Quan tity Caps	% of Qua ntity Cap	% of Quanti ty Capsu	% of Quant ity Caps	Mean % of Quanti ty	% of Quanti ty SD	% of Quan tity %CV	M value for AV	AV (Acc eptan ce	Judge	Kanazaw a Univ. Quantity test	Judge
			Kanazawa Univ. Content uniformity test (2nd stage)														idual content of is less than [1-(0.01)(25)]M nor more than [1												90.0≦mean≦110.0	
##	B-016	B-016/MM14/Y																									8.1	Pass	103.4	Pass
32	A-113	A113/MM14/YC																									14.2	Pass	97.6	Pass
##	B-074	B-074/MM14/Y																									49.7	Fail	78.4	Fail
9	A-021	A021/MM14/YC																									14.4	Pass	97.0	Pass
21	A-066	A066/MM14/YC																									11.5	Pass	99.9	Pass
##	B-012	B-012/MM14/Y																									7.7	Pass	104.7	Pass
##	B-043	B-043/MM14/Y																									9.3	Pass	106.0	Pass
##	B-046	B-046/MM14/Y																									2.1	Pass	107.0	Pass
##	B-071	B-071/MM14/Y																									11.9	Pass	97.8	Pass
##	B-078	B-078/MM14/Y																									11.2	Pass	98.5	Pass
1	PA-004	PA004/MM14/Y																									11.6	Pass	100.9	Pass

Appendix 11: Dissolution test results of omeprazole collected from Myanmar in 2014

1st stage



ID	Serial N	Sample Code	Kanazawa Univ. Dissolution test BP: 1st stage (Acid resistance Stage– No individual va										Kanazawa Univ. Dissolution test BP: Buffer Stage– No unit is less than Q+5% (Q=65%)										Disso Final Judge
			% of Quantity Capsule	% of Quantity Capsule	% of Quantity Capsule	% of Quantity Capsule 5	% of Quantity Capsule 5	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule	% of Quantity Capsule	% of Quantity Capsule 3	% of Quantity Capsule	% of Quantity Capsule 5	% of Quantity Capsule 6	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	
4	A-001	A001/MM14/YG	9.8	5.9	9.3	6.9	7.4	7.8	1.5	19.1	Pass	78.8	79.3	71.4	72.4	71.1	70.8	73.1	3.9	5.4	Pass	pass
5	A-002	A002/MM14/YG	3.0	2.7	2.6	2.5	4.0	2.9	0.6	19.1	Pass	96.9	99.5	98.2	96.1	96.4	98.4	97.6	1.3	1.4	Pass	pass
6	A-011	A011/MM14/YG	2.7	2.6	3.1	2.7	2.9	2.8	0.2	7.0	Pass	93.5	91.0	92.9	89.3	92.8	94.3	92.3	1.8	2.0	Pass	pass
7	A-012	A012/MM14/YG	7.2	5.7	5.0	7.1	5.8	6.0	1.0	16.2	Pass	80.0	74.7	91.1	80.0	76.4	90.3	82.1	7.0	8.5	Pass	pass
8	A-015	A015/MM14/YG	14.3	9.3	16.8	15.2	15.9	13.5	3.2	23.9	Fail	56.6	70.7	55.2	54.5	48.1	74.7	60.0	10.4	17.3	Fail	Fail
10	A-026	A026/MM14/YG	9.6	3.6	3.6	3.9	5.8	5.1	2.3	46.0	Pass	86.9	72.9	75.2	76.9	75.4	86.8	79.0	6.2	7.9	Pass	Pass
11	A-033	A033/MM14/YG	8.3	8.4	8.3	8.6	8.9	8.5	0.3	3.0	Pass	67.6	81.2	79.8	80.6	68.5	68.2	74.3	6.8	9.2	Fail	Fail
12	A-034	A034/MM14/YG	26.9	27.7	27.7	27.8	28.1	26.9	1.7	6.3	Fail	52.1	53.8	47.6	51.8	50.9	48.5	50.8	2.3	4.6	Fail	Fail
13	A-038	A038/MM14/YG	12.5	11.6	12.6	13.0	14.1	13.1	1.2	9.5	Fail	85.4	84.1	83.3	81.7	85.2	83.6	83.9	1.3	1.6	Pass	Fail
14	A-039	A039/MM14/YG	9.5	8.5	14.7	14.6	13.1	14.5	2.8	22.1	Fail	73.9	77.7	62.1	75.0	60.7	60.8	68.4	8.0	11.6	Fail	Fail
15	A-041	A041/MM14/YG	12.0	25.0	11.5	11.8	24.9	16.1	6.8	42.4	Fail	59.7	98.8	61.0	59.7	98.7	61.4	73.2	19.8	27.1	Fail	Fail
16	A-042	A042/MM14/YG	5.6	5.0	3.6	3.8	5.0	4.7	0.8	17.2	Pass	97.9	95.6	97.7	95.1	96.2	95.7	96.4	1.2	1.2	Pass	Pass
17	A-050	A050/MM14/YG	10.5	9.2	20.2	17.3	17.9	16.6	5.8	34.9	Fail	75.3	75.8	60.7	73.7	63.2	74.1	70.5	6.7	9.5	Fail	Fail
18	A-060	A060/MM14/YG	2.4	2.5	4.4	2.9	2.9	2.9	0.7	24.9	Pass	99.3	98.1	98.6	95.4	99.0	98.0	98.1	1.4	1.4	Pass	Pass
19	A-061	A061/MM14/YG	9.9	9.5	9.5	9.1	9.9	9.6	0.8	3.5	Pass	76.8	68.0	70.6	76.9	71.1	76.5	73.3	3.9	5.3	Fail	Fail
20	A-065	A065/MM14/YG	9.2	9.2	9.1	9.8	7.0	8.6	1.1	13.3	Pass	72.5	72.1	67.3	67.6	73.4	72.5	70.9	2.7	3.8	Fail	Fail
22	A-067	A067/MM14/YG	3.3	9.0	9.0	8.0	5.1	7.3	2.5	33.8	Pass	82.2	71.8	73.5	86.2	70.2	76.3	76.7	6.3	8.2	Pass	Pass
23	A-076	A076/MM14/YG	1.4	1.4	1.4	1.4	1.4	1.4	0.0	0.0	Pass	82.7	94.3	95.4	96.0	95.4	96.1	93.3	5.2	5.6	Pass	Pass
24	A-078	A078/MM14/YG	23.0	34.4	17.1	28.3	33.1	24.6	7.6	31.1	Fail	49.4	43.5	50.8	49.9	44.1	50.9	48.1	3.4	7.1	Fail	Fail
25	A-084	A084/MM14/YG	9.9	9.5	7.3	9.6	9.7	9.3	1.0	10.8	Pass	77.0	79.8	80.1	94.3	94.4	95.4	86.8	8.7	10.0	Pass	Pass
26	A-091	A091/MM14/YG	2.7	3.2	4.7	4.7	2.8	3.6	0.9	24.7	Pass	89.9	93.5	95.8	99.9	95.9	98.2	95.5	3.5	3.7	Pass	Pass
27	A-096	A096/MM14/YG	22.3	10.4	8.9	11.6	9.6	12.2	5.0	41.4	Fail	51.3	79.2	76.0	65.2	77.9	70.0	70.0	10.5	15.1	Fail	Fail
28	A-097	A097/MM14/YG	2.8	2.7	6.7	2.6	2.7	3.5	1.6	46.1	Pass	94.6	95.2	78.9	96.5	80.6	82.9	88.1	8.1	9.2	Pass	Pass
29	A-101	A101/MM14/YG	8.9	12.5	9.4	14.3	11.1	11.7	2.3	19.8	Fail	77.6	69.5	77.7	55.7	66.9	53.7	66.9	10.4	15.5	Fail	Fail
30	A-106	A106/MM14/YG	1.9	1.9	1.9	1.9	1.9	1.9	0.0	0.0	Pass	69.0	73.1	66.6	71.7	67.5	72.5	70.1	2.8	3.9	Fail	Fail
31	A-107	A107/MM14/YG	4.8	4.7	4.6	4.5	4.6	4.4	4.6	0.1	3.3	Pass	18.3	19.5	17.9	18.5	18.9	18.8	18.6	0.6	3.0	Fail	Fail
33	A-114	A114/MM14/YG	1.9	1.9	1.9	1.9	1.9	1.9	0.0	0.0	Pass	69.4	67.9	75.2	67.4	67.6	72.5	70.0	3.2	4.5	Fail	Fail

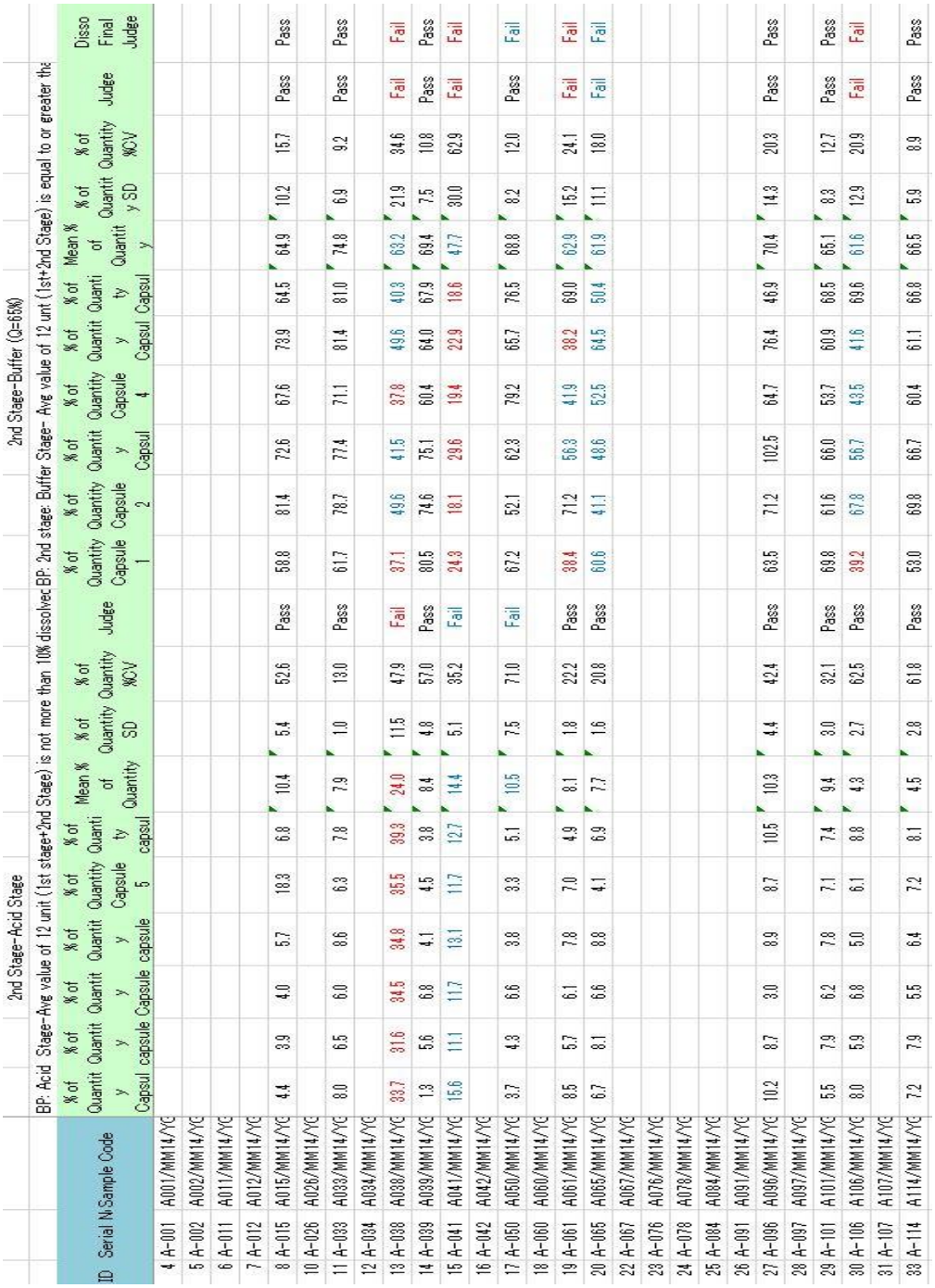
ID	Serial N	Sample Code	% of Quantity Capsul	% of Quantity Capsul	% of Quantity Capsu	% of Quantity Capsul	% of Quantity Capsule 5	% of Quantity Capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule	% of Quantity Capsule	% of Quantity Capsule 3	% of Quantity Capsule	% of Quantity Capsule 5	% of Quantity Capsule 6	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	Disso Final Judge
##	B-005	B-005/MM14/Y	6.0	3.6	3.6	3.9	5.8	4.1	4.5	1.1	24.6	Pass	96.0	92.6	95.2	91.6	94.0	95.8	94.2	1.8	1.9	Pass	Pass
##	B-006	B-006/MM14/Y	5.8	2.9	5.3	9.1	8.8	8.7	6.8	2.5	37.1	Pass	54.7	72.7	57.1	31.1	34.2	27.9	46.3	17.9	38.7	Fail	Fail
##	B-007	B-007/MM14/Y	39.9	38.1	42.5	40.3	39.5	42.3	40.4	1.7	4.2	Fail	49.5	49.7	63.4	55.7	50.7	50.7	53.3	5.5	10.2	Fail	Fail
##	B-008	B-008/MM14/Y	14.4	13.3	14.5	14.4	8.4	11.0	12.7	2.5	19.6	Fail	70.3	67.7	78.1	72.3	77.4	74.8	72.6	3.4	4.7	Fail	Fail
##	B-011	B-011/MM14/Y	5.3	4.0	7.2	4.4	7.2	5.4	5.6	1.4	24.2	Pass	96.6	97.9	98.3	66.4	98.5	97.3	92.5	12.8	13.9	Pass	Pass
##	B-013	B-013/MM14/Y	16.5	15.9	8.5	15.0	10.6	15.9	13.7	3.4	24.4	Fail	50.2	47.5	80.7	58.6	68.2	56.9	60.4	12.3	20.4	Fail	Fail
##	B-015	B-015/MM14/Y	17.9	17.2	17.7	18.0	17.5	17.7	17.7	0.3	1.7	Fail	39.7	38.5	42.8	39.8	38.9	42.6	40.4	1.9	4.6	Fail	Fail
##	B-017	B-017/MM14/Y	2.6	2.4	1.8	1.3	1.2	1.0	1.7	0.6	37.4	Pass	99.6	98.6	98.8	97.7	97.4	94.6	97.8	1.8	1.8	Pass	Pass
##	B-036	B-036/MM14/Y	8.8	7.6	1.0	1.2	0.9	8.0	4.6	3.9	85.4	Pass	78.3	70.7	78.4	69.3	68.3	66.6	71.9	5.1	7.1	Fail	Fail
##	B-037	B-037/MM14/Y	3.5	7.1	5.1	4.2	6.8	5.0	5.3	1.4	26.7	Pass	92.2	86.9	87.1	91.1	88.9	92.9	89.9	2.6	2.9	Pass	Pass
##	B-045	B-045/MM14/Y	2.6	3.0	4.4	2.5	2.8	4.4	3.3	0.9	26.6	Pass	71.7	94.3	86.6	73.1	93.9	86.8	84.4	9.9	11.7	Pass	Pass
##	B-049	B-049/MM14/Y	2.3	2.5	2.7	0.9	0.9	0.9	1.7	0.9	54.1	Pass	66.4	85.3	84.9	65.6	83.7	66.3	75.4	10.2	13.5	Fail	Fail
##	B-054	B-054/MM14/Y	22.8	26.4	28.2	24.0	25.3	27.4	25.7	2.1	8.0	Fail	31.4	32.1	35.5	31.8	73.9	73.2	46.3	21.2	45.7	Fail	Fail
##	B-059	B-059/MM14/Y	2.3	2.2	2.7	2.3	2.5	2.6	2.4	0.2	8.2	Pass	93.9	97.7	99.8	93.3	93.4	91.2	94.9	3.2	3.4	Pass	Pass
##	B-065	B-065/MM14/Y	11.1	11.3	10.9	11.0	11.2	10.9	11.1	0.2	1.7	Fail	56.0	52.7	47.6	56.4	54.1	48.6	52.6	3.7	7.1	Fail	Fail
##	B-070	B-070/MM14/Y	3.7	3.9	3.8	2.5	3.1	2.5	3.3	0.6	19.7	Pass	82.7	94.3	93.5	94.2	95.4	95.7	92.7	4.9	5.3	Pass	Pass
##	B-077	B-077/MM14/Y	1.4	1.4	1.4	1.4	1.4	1.4	1.4	0.0	0.0	Pass	87.1	86.9	87.2	86.4	88.0	87.9	87.2	0.6	0.7	Pass	Pass
##	B-090	B-090/MM14/Y	2.2	1.9	1.9	2.0	2.0	2.0	2.0	0.1	6.4	Pass	77.0	79.8	80.1	81.4	80.1	77.2	79.3	1.8	2.2	Pass	Pass
##	B-092	B-092/MM14/Y	2.5	2.4	1.8	1.1	1.2	1.2	1.7	0.6	36.5	Pass	92.8	95.2	98.8	97.5	97.3	94.7	96.0	2.2	2.3	Pass	Pass
##	B-098	B-098/MM14/Y	2.4	2.3	2.5	2.4	2.2	2.4	2.3	0.1	4.6	Pass	81.6	92.7	89.7	83.0	93.3	91.8	88.7	5.1	5.8	Pass	Pass
##	B-106	B106/MM14/YG	12.4	7.6	14.8	20.7	19.3	20.7	15.9	5.3	33.1	Fail	49.7	47.1	79.3	48.8	77.9	77.0	63.3	16.2	25.6	Fail	Fail
##	B-108	B108/MM14/YG	3.5	7.2	4.9	4.2	6.9	4.9	5.3	1.5	28.3	Pass	92.2	87.5	87.3	91.2	88.4	92.3	89.8	2.3	2.6	Pass	Pass
##	B-110	B110/MM14/YG	24.4	25.4	25.1	24.7	25.4	21.1	24.4	1.7	6.8	Fail	53.6	62.8	62.1	52.8	53.4	62.6	57.9	5.1	8.8	Fail	Fail
2	PA-005	PA005/MM14/Y	26.9	9.3	15.9	26.6	9.3	16.7	17.3	7.9	45.6	Fail	60.1	65.2	61.7	60.1	65.1	61.7	62.3	2.3	3.7	Fail	Fail
3	PA-006	PA006/MM14/Y	5.4	4.0	7.2	4.4	7.2	5.5	5.6	1.4	24.2	Pass	83.1	84.9	82.2	82.7	83.6	82.1	83.1	1.0	1.2	Pass	pass
##	PB-002	PB-002/MM14/	11.0	18.1	11.0	17.7	18.2	11.2	14.5	3.8	26.1	Fail	51.5	60.6	59.9	50.7	51.3	60.4	55.7	5.0	9.0	Fail	Fail
##	PB-003	PB-003/MM14/	9.0	8.9	8.9	5.7	3.4	5.1	6.8	2.4	35.4	Pass	30.7	34.4	26.5	54.9	71.2	57.6	45.9	17.9	39.0	Fail	Fail

Kanazawa Univ. Dissolution test BP: 1st stage (Acid resistance Stage- No individual va Kanazawa Univ. Dissolution test BP: Buffer Stage- No unit is less than Q+5% (Q=65%)

ID	Serial N	Sample Code	% of Quantity Capsul	% of Quantity Capsul	% of Quantity Capsu	% of Quantity Capsul	% of Quantity Capsule 5	% of Quantity Capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule	% of Quantity Capsule	% of Quantity Capsule 3	% of Quantity Capsule	% of Quantity Capsule 5	% of Quantity Capsule 6	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	Disso Final Judge
Kanazawa Univ. Dissolution test USP: 1st stage (Acid resistance Stage- No individual v Kanazawa Univ. Dissolution test USP: Buffer Stage- No unit is less than Q+5% (Q=75%)																							
##	B-016	B-016/MM14/Y	10.9	10.8	4.0	2.8	8.9	6.9	7.4	3.5	46.8	Pass	89.4	87.9	90.5	92.6	92.2	89.5	90.3	1.8	2.0	Pass	Pass
32	A-113	A113/MM14/YG	17.1	11.2	7.8	17.6	16.7	15.3	14.3	3.9	27.6	Fail	81.2	77.6	80.0	78.6	77.3	75.9	78.4	1.9	2.5	Fail	Fail
##	B-074	B-074/MM14/Y	14.3	11.3	14.3	10.7	14.1	14.4	13.2	1.7	12.9	Pass	77.1	81.7	80.0	78.6	81.4	77.7	79.4	1.9	2.4	Fail	Fail
9	A-021	A021/MM14/YG	2.0	4.6	3.7	0.5	2.9	4.5	3.0	1.6	52.7	Pass	86.1	95.4	95.7	96.3	88.0	93.2	92.4	4.3	4.7	Pass	Pass
21	A-066	A066/MM14/YG	11.7	5.3	1.8	12.2	11.3	9.8	8.7	4.2	48.5	Pass	88.8	89.9	98.9	91.0	91.7	95.9	92.7	3.9	4.2	Pass	Pass
##	B-012	B-012/MM14/Y	4.3	8.4	6.1	9.8	7.9	8.0	7.4	2.0	26.3	Pass	92.8	97.9	93.9	90.9	92.7	97.6	94.3	2.9	3.0	Pass	Pass
##	B-043	B-043/MM14/Y	5.8	8.3	4.0	1.6	14.0	4.4	6.3	4.3	68.4	Pass	90.7	85.0	90.3	89.7	90.1	91.9	89.6	2.4	2.7	Pass	Pass
##	B-046	B-046/MM14/Y	0.8	1.8	1.6	5.8	4.5	6.9	3.6	2.5	70.0	Pass	83.4	89.1	86.9	88.0	85.5	88.4	86.9	2.1	2.5	Pass	Pass
##	B-071	B-071/MM14/Y	0.6	12.5	6.3	10.1	4.8	2.2	6.1	4.6	75.1	Pass	88.4	89.2	86.4	87.5	93.3	87.8	88.8	2.4	2.7	Pass	Pass
##	B-078	B-078/MM14/Y	1.2	1.3	3.4	2.7	1.4	13.5	3.9	4.8	122.3	Pass	85.6	89.2	86.5	87.5	90.0	87.6	87.7	1.6	1.9	Pass	Pass
1	PA-004	PA004/MM14/Y	12.6	11.2	12.6	12.8	13.2	11.4	12.3	0.8	6.7	Pass	89.4	90.4	99.5	91.6	92.2	96.4	93.2	3.9	4.2	Pass	Pass

Appendix 12: Dissolution test results of omeprazole collected from Myanmar in 2014

2nd stage



ID	Serial N	Sample Code	2nd Stage-Acid Stage										2nd Stage-Buffer (Q=65%)												
			BP: Acid Stage-Avg value of 12 unit (1st stage+2nd Stage) is not more than 10% dissolvec										BP: 2nd stage: Buffer Stage- Avg value of 12 unit (1st+2nd Stage) is equal to or greater tha												
			% of Quantity Capsule	% of Quantity capsule	% of Quantity Capsule	% of Quantity Capsule 5	% of Quanti ty capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsul y	% of Quantity Capsule 4	% of Quantity Capsul y	% of Quanti ty Capsul	Mean % of Quantit y	% of Quantit y SD	% of Quantity %CV	Judge	Disso Final Judge
4	A-001	A001/MM14/YG																							
5	A-002	A002/MM14/YG																							
6	A-011	A011/MM14/YG																							
7	A-012	A012/MM14/YG																							
8	A-015	A015/MM14/YG	4.4	3.9	4.0	5.7	18.3	6.8	10.4	5.4	52.6	Pass	58.8	81.4	72.6	67.6	73.9	64.5	64.9	10.2	15.7	Pass	Pass
10	A-026	A026/MM14/YG																							
11	A-033	A033/MM14/YG	8.0	6.5	6.0	8.6	6.3	7.8	7.9	1.0	13.0	Pass	61.7	78.7	77.4	71.1	81.4	81.0	74.8	6.9	9.2	Pass	Pass
12	A-034	A034/MM14/YG																							
13	A-038	A038/MM14/YG	33.7	31.6	34.5	34.8	35.5	39.8	24.0	11.5	47.9	Fail	37.1	49.6	41.5	37.8	49.6	40.8	63.2	21.9	34.6	Fail	Fail
14	A-039	A039/MM14/YG	1.3	5.6	6.8	4.1	4.5	3.8	8.4	4.8	57.0	Pass	80.5	74.6	75.1	60.4	64.0	67.9	69.4	7.5	10.8	Pass	Pass
15	A-041	A041/MM14/YG	15.6	11.1	11.7	13.1	11.7	12.7	14.4	5.1	35.2	Fail	24.9	18.1	29.6	19.4	22.9	18.6	47.7	30.0	62.9	Fail	Fail
16	A-042	A042/MM14/YG																							
17	A-050	A050/MM14/YG	3.7	4.3	6.6	3.8	3.3	5.1	10.5	7.5	71.0	Fail	67.2	52.1	62.3	79.2	65.7	76.5	68.8	8.2	12.0	Pass	Fail
18	A-060	A060/MM14/YG																							
19	A-061	A061/MM14/YG	8.5	5.7	6.1	7.8	7.0	4.9	8.1	1.8	22.2	Pass	38.4	71.2	56.3	41.9	38.2	69.0	62.9	15.2	24.1	Fail	Fail
20	A-065	A065/MM14/YG	6.7	8.1	6.6	8.8	4.1	6.9	7.7	1.6	20.8	Pass	60.6	41.1	48.6	52.5	64.5	50.4	61.9	11.1	18.0	Fail	Fail
22	A-067	A067/MM14/YG																							
23	A-076	A076/MM14/YG																							
24	A-078	A078/MM14/YG																							
25	A-084	A084/MM14/YG																							
26	A-091	A091/MM14/YG																							
27	A-096	A096/MM14/YG	10.2	8.7	3.0	8.9	8.7	10.5	10.3	4.4	42.4	Pass	63.5	71.2	102.5	64.7	78.4	46.9	70.4	14.3	20.3	Pass	Pass
28	A-097	A097/MM14/YG																							
29	A-101	A101/MM14/YG	5.5	7.9	6.2	7.8	7.1	7.4	9.4	3.0	32.1	Pass	69.8	61.6	66.0	53.7	60.9	68.5	65.1	8.3	12.7	Pass	Pass
30	A-106	A106/MM14/YG	8.0	5.9	6.8	5.0	6.1	8.8	4.3	2.7	62.5	Pass	39.2	67.8	56.7	43.5	41.6	69.6	61.6	12.9	20.9	Fail	Fail
31	A-107	A107/MM14/YG																							
33	A-114	A114/MM14/YG	7.2	7.9	5.5	6.4	7.2	8.1	4.5	2.8	61.8	Pass	53.0	69.8	66.7	60.4	61.1	66.8	66.5	5.9	8.9	Pass	Pass

			2nd Stage-Acid Stage										2nd Stage-Buffer (Q=65%)									
			BP: Acid Stage-Avg value of 12 unit (1st stage+2nd Stage) is not more than 10% dissolvec										BP: 2nd stage: Buffer Stage- Avg value of 12 unt (1st+2nd Stage) is equal to or greater tha									
ID	Serial N	Sample Code	% of Quantity Capsul	% of Quantity capsule	% of Quantity Capsule	% of Quantity capsule	% of Quantity Capsule 5	% of Quantity capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsul	% of Quantity Capsule 4	% of Quantity Capsul	% of Quantity Capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	Disso Final Judge
##	B-005	B-005/MM14/Y																					
##	B-006	B-006/MM14/Y																					
##	B-007	B-007/MM14/Y																					
##	B-008	B-008/MM14/Y	7.0	6.5	8.8	4.3	6.9	8.4	9.8	3.6	36.4	Pass	63.3	52.7	60.6	51.7	42.5	50.0	63.0	11.4	18.2	Fail	Fail
##	B-011	B-011/MM14/Y																					
##	B-013	B-013/MM14/Y	3.8	6.8	3.9	5.1	3.6	4.6	9.2	5.3	58.0	Pass	65.6	54.7	62.1	63.1	63.3	64.9	61.3	8.8	14.3	Fail	Fail
##	B-015	B-015/MM14/Y																					
##	B-017	B-017/MM14/Y																					
##	B-036	B-036/MM14/Y	8.8	10.7	9.1	10.0	8.2	12.8	7.3	4.0	55.2	Pass	74.9	64.9	61.2	65.5	62.3	75.3	69.6	5.9	8.5	Pass	Pass
##	B-037	B-037/MM14/Y																					
##	B-045	B-045/MM14/Y																					
##	B-049	B-049/MM14/Y	8.0	7.5	6.8	6.7	6.4	7.8	4.4	3.0	67.2	Pass	65.6	72.1	81.4	78.6	78.2	80.4	75.7	8.0	10.5	Pass	Pass
##	B-054	B-054/MM14/Y																					
##	B-059	B-059/MM14/Y																					
##	B-065	B-065/MM14/Y	7.8	8.3	6.8	7.7	6.8	9.5	9.4	1.8	19.4	Pass	71.2	64.9	74.5	64.9	73.3	61.8	60.5	9.4	15.5	Fail	Fail
##	B-070	B-070/MM14/Y																					
##	B-077	B-077/MM14/Y																					
##	B-090	B-090/MM14/Y																					
##	B-092	B-092/MM14/Y																					
##	B-098	B-098/MM14/Y																					
##	B-106	B106/MM14/YG	12.0	16.3	11.1	12.1	14.2	11.2	14.4	4.1	28.8	Fail	34.0	27.7	31.1	32.4	28.6	26.2	46.6	20.7	44.3	Fail	Fail
##	B-108	B108/MM14/YG																					
##	B-110	B110/MM14/YG	25.0	25.8	22.1	26.5	27.9	32.4	25.5	2.8	11.1	Fail	35.2	34.1	32.5	34.1	35.7	37.1	46.3	12.6	27.2	Fail	Fail
2	PA-005	PA005/MM14/Y																					
3	PA-006	PA006/MM14/Y																					
##	PB-002	PB-002/MM14/	11.6	3.0	13.5	12.7	11.0	12.3	12.6	4.2	33.0	Fail	61.8	90.6	60.5	64.9	57.5	53.4	60.2	10.7	17.7	Fail	Fail
##	PB-003	PB-003/MM14/																					

			2nd Stage-Acid Stage										2nd Stage-Buffer (Q=65%)									
			BP: Acid Stage-Avg value of 12 unit (1st stage+2nd Stage) is not more than 10% dissolvec										BP: 2nd stage: Buffer Stage- Avg value of 12 unt (1st+2nd Stage) is equal to or greater tha									
ID	Serial N	Sample Code	% of Quantity Capsul	% of Quantity capsule	% of Quantity Capsule	% of Quantity capsule	% of Quantity Capsule 5	% of Quantity capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Capsule 1	% of Quantity Capsule 2	% of Quantity Capsul	% of Quantity Capsule 4	% of Quantity Capsul	% of Quantity Capsul	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	Disso Final Judge
			2nd Stage-Acid Stage										2nd Stage-Buffer (Q=75%)									
			USP: Acid Stage-Avg value of 12 unit (1st stage+2nd Stage) is not more than 20% dissolve										USP: 2nd stage: Buffer Stage- Avg value of 12 unt (1st+2nd Stage) is equal to or greater th									
##	B-016	B-016/MM14/Y																					
32	A-113	A113/MM14/YG	7.7	2.2	0.3	3.1	0.3	5.2	8.7	6.7	76.8	Pass	100.8	102.5	109.9	116.5	101.8	105.6	92.3	15.1	16.4	Pass	Pass
##	B-074	B-074/MM14/Y	2.6	2.9	1.9	1.8	0.7	0.6	7.5	6.1	81.7	Pass	90.6	103.7	94.0	96.5	100.9	85.1	87.3	9.5	10.9	Pass	Pass
9	A-021	A021/MM14/YG																					
21	A-066	A066/MM14/YG																					
##	B-012	B-012/MM14/Y																					
##	B-043	B-043/MM14/Y																					
##	B-046	B-046/MM14/Y																					
##	B-071	B-071/MM14/Y																					
##	B-078	B-078/MM14/Y																					
1	PA-004	PA004/MM14/Y																					

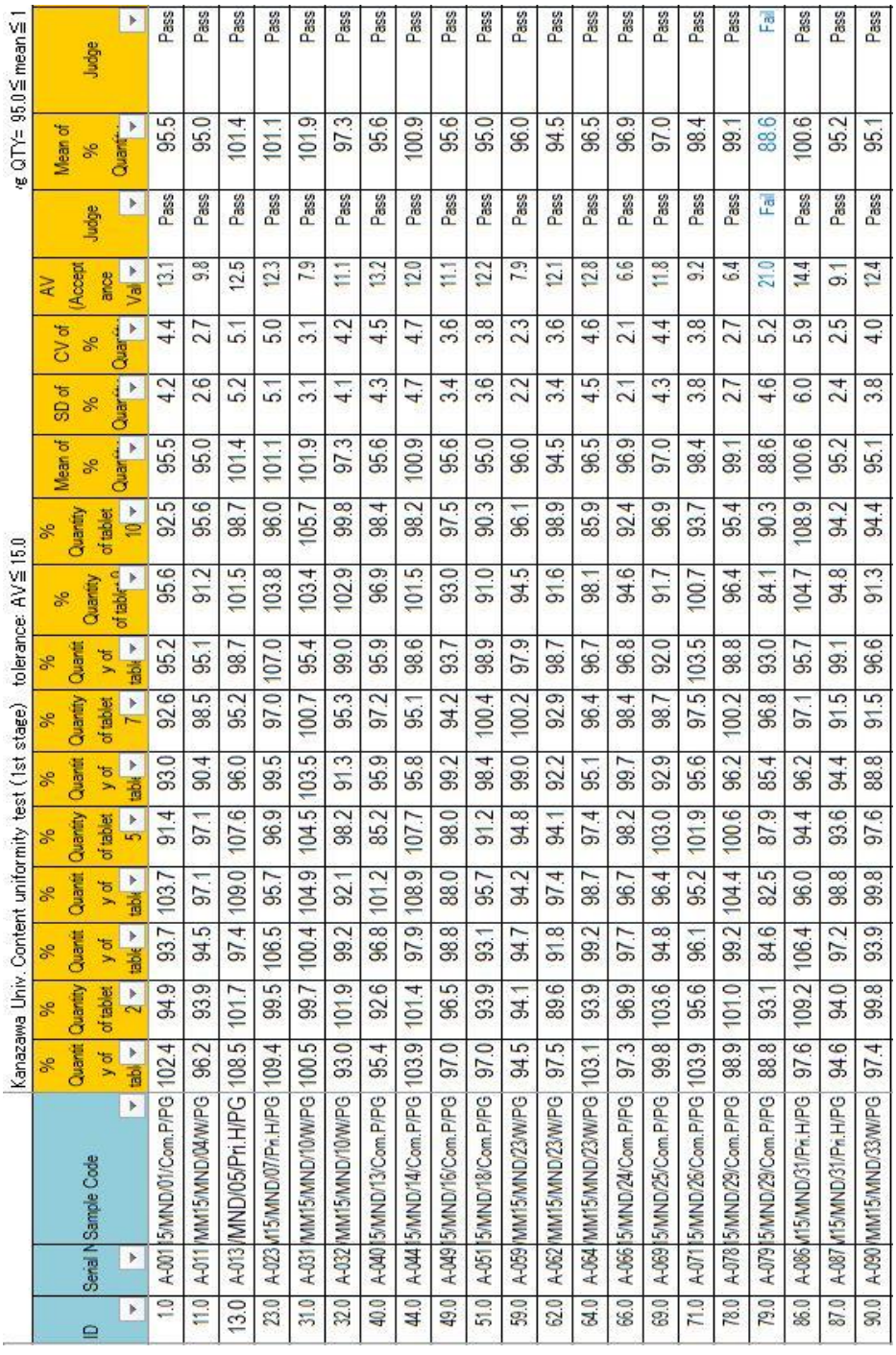
Appendix 13: Dissolution test results of omeprazole collected from Myanmar in 2014

3rd stage

			3rd Stage-Acid																3rd Stage-Buffer (Q=65%)															
			lue of 24 units (1st+2nd+3rd Stage) is not more than 10% dissloved & no individual unit is great																units (1st+2nd+3rd Stage) is equal to or greater than Q(Q=65%), not more than 2 units are less tha															
ID	Serial N	Sample Code	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Cap	% of Quantity Cap	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Capsu	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	% of Quantity Caps	Mean % of Quantity	% of Quantity SD	% of Quantity %CV	Judge
17	A-050	A050/MM14/^	4.2	5.5	4.2	5.4	5.1	5.6	4.2	4.5	4.0	4.6	4.4	4.1	7.6	6.0	78.9	Pass	81.9	73.5	75.1	62.4	68.6	45.0	72.9	76.6	74.0	60.0	65.6	68.2	68.7	8.8	12.8	Pass
20	A-065	A065/MM14/^	5.1	6.8	4.8	26.3	5.2	8.3	6.4	4.0	5.8	5.9	5.9	6.9	7.7	4.3	55.8	Pass	81.0	51.8	67.7	55.4	82.7	66.2	64.8	87.1	71.7	71.1	49.9	60.1	64.7	11.7	18.1	Pass
##	B-008	B-008/MM14/	7.8	8.5	7.6	3.7	6.9	7.7	3.8	7.2	7.9	6.8	7.7	8.4	8.4	3.1	36.4	Pass	68.1	56.7	59.2	65.1	82.4	71.7	57.8	89.6	80.8	51.5	77.5	58.4	65.6	11.8	18.0	pass
##	B-013	B-013/MM14/	7.5	6.2	5.0	6.7	6.9	7.3	6.9	6.0	7.6	6.9	4.8	6.7	7.9	4.0	50.4	Pass	73.1	64.5	84.0	59.9	72.4	81.4	67.6	62.7	61.4	69.8	66.7	62.2	65.1	8.9	13.8	Pass
##	B-065	B-065/MM14/	8.5	10.2	8.3	8.4	8.1	8.7	8.4	9.0	8.1	8.2	10.6	8.5	9.1	1.4	15.7	Pass	64.6	58.7	68.4	63.2	71.5	66.9	60.1	61.7	74.7	66.2	66.5	66.1	63.1	7.7	12.2	Fail
##	PB-002	PB-002/MM1	10.4	10.9	9.8	10.1	10.6	10.3	10.2	7.8	8.3	8.0	8.5	10.1	11.1	3.4	30.3	Fail	59.6	74.3	60.1	69.3	73.4	68.3	55.2	77.7	57.5	71.6	65.9	68.6	63.5	9.5	15.0	Fail

Appendix 14: Quantity and content uniformity test results of pioglitazone HCl collected from Myanmar in 2015

1st stage



Kanazawa Univ. Content uniformity test (1st stage) tolerance: AV≦15.0 g QTY= 95.0≦mean≦1

ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 5	% Quantity of tablet 7	% Quantity of tablet 8	% Quantity of tablet 10	Mean of % Quantity	SD of % Quantity	CV of % Quantity	AV (Acceptance Val	Judge	Mean of % Quantity	Judge
1.0	A-001	15/MND/01/Com.P/PG	102.4	94.9	93.7	91.4	92.6	95.2	92.5	95.5	4.2	4.4	13.1	Pass	95.5	Pass
11.0	A-011	MM15/MND/04/W/PG	96.2	93.9	94.5	97.1	98.5	95.1	95.6	95.0	2.6	2.7	9.8	Pass	95.0	Pass
13.0	A-013	MND/05/Pri.H/PG	108.5	101.7	97.4	107.6	95.2	98.7	98.7	101.4	5.2	5.1	12.5	Pass	101.4	Pass
23.0	A-023	M15/MND/07/Pri.H/PG	109.4	99.5	106.5	96.9	97.0	107.0	96.0	101.1	5.1	5.0	12.3	Pass	101.1	Pass
31.0	A-031	MM15/MND/10/W/PG	100.5	99.7	100.4	104.5	100.7	95.4	105.7	101.9	3.1	3.1	7.9	Pass	101.9	Pass
32.0	A-032	MM15/MND/10/W/PG	93.0	101.9	99.2	98.2	95.3	99.0	99.8	97.3	4.1	4.2	11.1	Pass	97.3	Pass
40.0	A-040	15/MND/13/Com.P/PG	95.4	92.6	96.8	85.2	97.2	95.9	98.4	95.6	4.3	4.5	13.2	Pass	95.6	Pass
44.0	A-044	15/MND/14/Com.P/PG	103.9	101.4	97.9	107.7	95.1	98.6	98.2	100.9	4.7	4.7	12.0	Pass	100.9	Pass
49.0	A-049	15/MND/16/Com.P/PG	97.0	96.5	98.8	98.0	94.2	93.7	97.5	95.6	3.4	3.6	11.1	Pass	95.6	Pass
51.0	A-051	15/MND/18/Com.P/PG	97.0	93.9	93.1	91.2	100.4	98.9	90.3	95.0	3.6	3.8	12.2	Pass	95.0	Pass
59.0	A-059	MM15/MND/23/W/PG	94.5	94.1	94.7	94.8	100.2	97.9	96.1	96.0	2.2	2.3	7.9	Pass	96.0	Pass
62.0	A-062	MM15/MND/23/W/PG	97.5	89.6	91.8	94.1	92.9	98.7	98.9	94.5	3.4	3.6	12.1	Pass	94.5	Pass
64.0	A-064	MM15/MND/23/W/PG	103.1	93.9	99.2	97.4	96.4	96.7	85.9	96.5	4.5	4.6	12.8	Pass	96.5	Pass
66.0	A-066	5/MND/24/Com.P/PG	97.3	96.9	97.7	98.2	98.4	96.8	92.4	96.9	2.1	2.1	6.6	Pass	96.9	Pass
69.0	A-069	5/MND/25/Com.P/PG	99.8	103.6	94.8	103.0	98.7	92.0	96.9	97.0	4.3	4.4	11.8	Pass	97.0	Pass
71.0	A-071	15/MND/26/Com.P/PG	103.9	95.6	96.1	101.9	97.5	103.5	93.7	98.4	3.8	3.8	9.2	Pass	98.4	Pass
78.0	A-078	5/MND/29/Com.P/PG	98.9	101.0	99.2	100.6	100.2	98.8	95.4	99.1	2.7	2.7	6.4	Pass	99.1	Pass
79.0	A-079	15/MND/29/Com.P/PG	88.8	93.1	84.6	87.9	96.8	93.0	90.3	88.6	4.6	5.2	21.0	Fail	88.6	Fail
86.0	A-086	M15/MND/31/Pri.H/PG	97.6	109.2	106.4	94.4	97.1	95.7	108.9	100.6	6.0	5.9	14.4	Pass	100.6	Pass
87.0	A-087	M15/MND/31/Pri.H/PG	94.6	94.0	97.2	93.6	91.5	99.1	94.2	95.2	2.4	2.5	9.1	Pass	95.2	Pass
90.0	A-090	MM15/MND/33/W/PG	97.4	99.8	93.9	97.6	91.5	96.6	94.4	95.1	3.8	4.0	12.4	Pass	95.1	Pass

Kanazawa Univ. Content uniformity test (1st stage) tolerance: AV≦ 15.0 ※ QTY= 95.0≦ mean ≦ 1

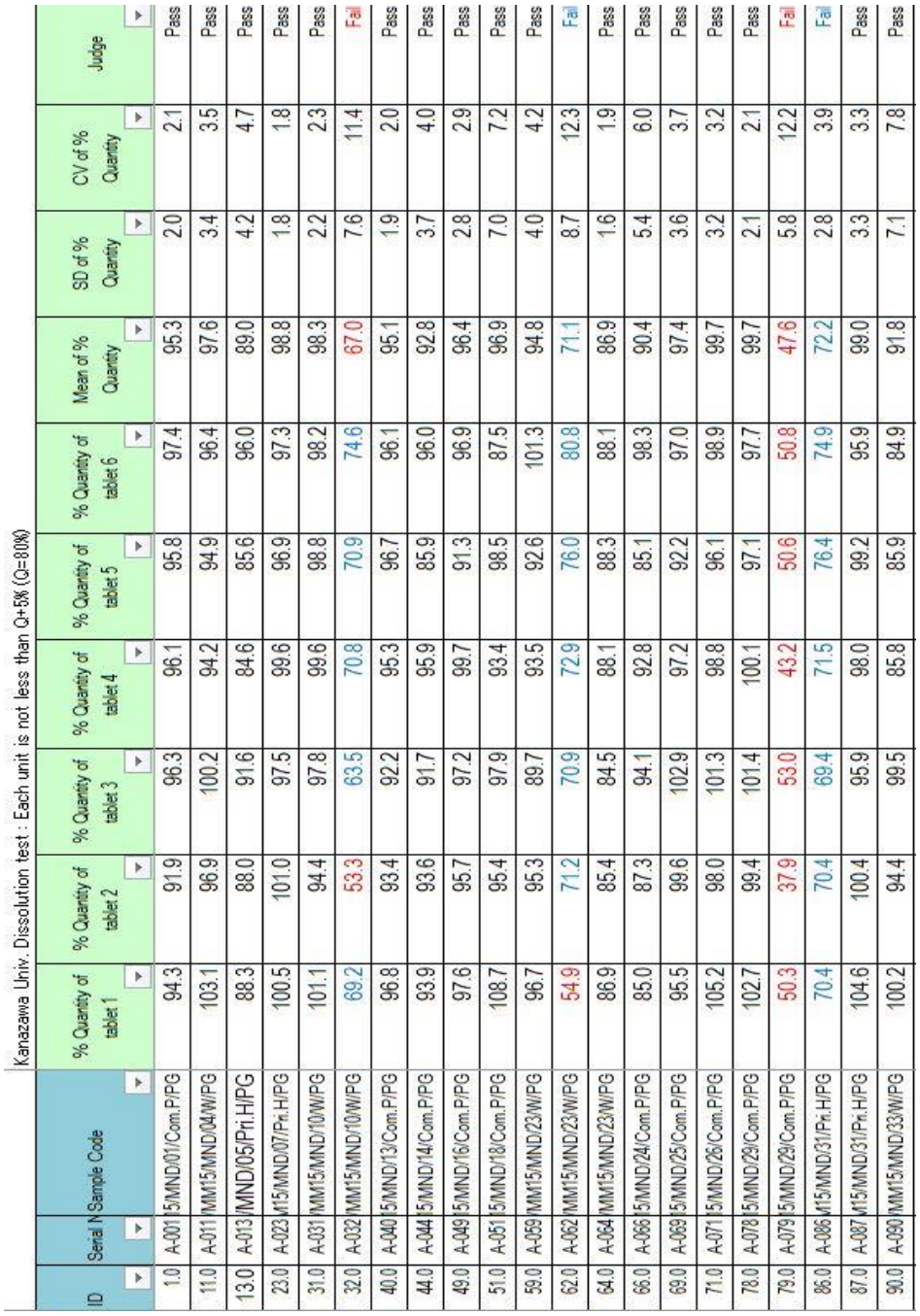
ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	% Quantity of tablet 7	% Quantity of tablet 8	% Quantity of tablet 9	% Quantity of tablet 10	Mean of % Quantity	SD of % Quantity	CV of % Quantity	AV (Acceptance Value)	Judge	Mean of % Quantity	Judge
101.0	A-101	15/MND/38/Com.P/PG	102.0	96.8	97.5	91.8	91.8	91.6	96.3	96.7	93.3	96.6	96.1	3.2	3.3	10.0	Pass	96.1	Pass
102.0	A-102	15/MND/39/Com.P/PG	102.7	99.8	95.8	98.0	96.4	98.5	93.2	91.6	98.4	92.7	96.7	3.5	3.6	10.1	Pass	96.7	Pass
103.0	A-103	MM15/MND/40/W/PG	102.0	102.0	98.2	107.1	105.5	96.4	95.4	103.7	99.5	99.5	100.9	3.8	3.8	9.3	Pass	100.9	Pass
104.0	A-104	15/MND/41/Com.P/PG	106.8	109.2	98.8	103.3	95.3	98.4	98.4	104.1	104.3	105.7	102.4	4.5	4.4	11.6	Pass	102.4	Pass
105.0	A-105	15/MND/42/Com.P/PG	97.4	91.2	95.8	95.7	93.1	96.7	96.6	99.0	94.7	93.0	95.3	2.3	2.5	8.8	Pass	95.3	Pass
106.0	A-106	15/MND/43/Com.P/PG	95.6	94.4	94.8	98.4	95.1	96.5	98.5	95.1	93.9	97.3	96.0	1.7	1.7	6.5	Pass	96.0	Pass
108.0	A-108	M15/MND/44/Pre.H/PG	108.3	102.1	96.2	98.9	98.4	96.1	96.0	103.5	102.3	98.3	100.0	4.0	4.0	9.5	Pass	100.0	Pass
117.0	B-009	M15/MND/03/Pre.H/PG	95.7	92.3	93.0	91.7	95.6	92.4	92.6	99.1	94.9	102.6	95.0	3.5	3.7	11.9	Pass	95.0	Pass
121.0	B-013	MND/04/Com.P/W/PG	104.3	101.6	102.1	97.1	93.5	99.1	103.1	97.0	99.1	98.1	99.5	3.3	3.3	7.9	Pass	99.5	Pass
123.0	B-015	MND/04/Com.P/W/PG	99.2	92.2	104.7	100.5	102.1	102.8	102.6	101.2	105.2	99.7	101.0	3.7	3.6	8.8	Pass	101.0	Pass
128.0	B-020	M15/MND/05/Cli.P/PG	99.4	90.3	95.3	90.8	90.3	103.5	102.3	93.3	95.3	103.0	96.4	5.3	5.5	14.9	Pass	96.4	Pass
137.0	B-029	15/MND/08/Com.P/PG	105.1	101.1	105.5	104.6	104.9	103.4	105.4	102.0	93.7	91.9	101.8	4.9	4.9	12.1	Pass	101.8	Pass
141.0	B-033	15/MND/10/Com.P/PG	94.8	97.3	98.2	97.2	95.9	95.8	95.6	95.5	95.4	96.7	96.2	1.1	1.1	4.8	Pass	96.2	Pass
142.0	B-034	15/MND/10/Com.P/PG	99.5	95.6	96.1	94.0	95.4	94.5	97.8	94.7	95.4	97.1	96.0	1.7	1.8	6.5	Pass	96.0	Pass
143.0	B-035	15/MND/10/Com.P/PG	100.2	97.8	98.9	100.9	95.6	98.5	97.1	98.7	90.7	95.6	97.4	2.9	3.0	8.1	Pass	97.4	Pass
164.0	B-056	M15/MND/16/Pre.H/PG	107.8	97.1	99.3	99.6	94.4	97.0	100.0	100.5	97.7	99.7	99.3	3.5	3.5	8.5	Pass	99.3	Pass
169.0	B-061	15/MND/19/Com.P/PG	103.3	99.9	98.1	105.0	106.0	100.2	103.9	107.3	107.5	96.5	102.8	3.9	3.8	10.6	Pass	102.8	Pass
170.0	B-062	MND/20/Com.P/W/PG	99.2	97.8	98.0	97.8	99.3	98.1	98.3	97.2	98.0	97.9	98.2	0.6	0.7	1.9	Pass	98.2	Pass
172.0	B-064	15/MND/21/Com.P/PG	104.8	109.3	102.2	103.8	95.7	99.1	108.4	104.2	104.7	100.2	103.2	4.1	4.0	11.7	Pass	103.2	Pass
174.0	B-066	15/MND/22/Com.P/PG	92.3	97.1	97.7	96.5	93.0	95.2	93.7	95.3	91.6	97.5	95.0	2.2	2.4	8.9	Pass	95.0	Pass
175.0	B-067	15/MND/23/Com.P/PG	92.1	97.8	100.8	92.9	99.0	99.7	94.8	97.6	93.1	95.7	96.4	3.1	3.2	9.5	Pass	96.4	Pass

Kanazawa Univ. Content uniformity test (1st stage) tolerance: AV≦ 15.0 ※ QTY= 95.0≦ mean ≦ 1

ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	% Quantity of tablet 7	% Quantity of tablet 8	% Quantity of tablet 9	% Quantity of tablet 10	Mean of % Quantity	SD of % Quantity	CV of % Quantity	AV (Acceptance Value)	Judge	Mean of % Quantity	Judge
177.0	B-069	M15/MND/25/Pre.H/PG	99.5	101.2	99.6	96.9	100.3	98.0	103.7	102.6	92.7	102.0	99.6	3.2	3.2	7.7	Pass	99.6	Pass
184.0	B-076	15/MND/29/Com.P/PG	96.4	97.7	96.0	102.9	94.2	95.4	98.9	97.2	94.2	94.9	96.8	2.6	2.7	8.0	Pass	96.8	Pass
186.0	B-078	15/MND/30/Com.P/PG	101.5	99.6	101.7	98.3	97.1	101.0	96.2	89.8	95.9	91.9	97.3	4.0	4.1	10.9	Pass	97.3	Pass
188.0	B-080	MND/32/Com.P/W/PG	91.7	103.1	99.8	100.3	99.3	97.8	97.8	104.0	91.2	99.7	98.5	4.2	4.3	10.1	Pass	98.5	Pass
190.0	B-082	15/MND/33/Com.P/PG	93.3	100.8	102.3	104.2	101.3	93.3	94.2	91.6	107.2	95.3	98.3	5.4	5.5	13.2	Pass	98.3	Pass
197.0	B-089	15/MND/36/Com.P/PG	94.0	93.5	93.4	100.5	91.0	96.8	93.3	94.1	97.5	92.9	94.7	2.8	2.9	10.5	Pass	94.7	Pass
198.0	B-090	15/MND/37/Com.P/PG	98.2	92.1	93.1	99.7	96.9	96.2	96.7	95.3	101.3	97.2	96.7	2.8	2.9	8.5	Pass	96.7	Pass
201.0	B-093	15/MND/37/Com.P/PG	105.3	98.2	97.1	96.5	98.6	96.1	99.3	87.6	104.1	96.4	97.9	4.8	4.9	12.2	Pass	97.9	Pass
202.0	B-094	5/MND/38/Com.P/PG	94.0	99.1	92.8	91.8	93.7	95.5	95.2	94.1	95.5	96.3	94.8	2.0	2.2	8.6	Pass	94.8	Pass
204.0	B-096	15/MND/39/Com.P/PG	101.7	95.0	97.1	99.0	95.4	91.3	97.5	94.1	97.7	95.3	96.4	2.8	3.0	8.9	Pass	96.4	Pass
207.0	B-099	15/MND/41/Com.P/PG	99.8	100.7	88.3	91.9	94.2	91.6	96.9	94.6	98.7	96.8	95.3	4.0	4.2	12.7	Pass	95.3	Pass
213.0	B-105	15/MND/44/Com.P/PG	102.3	98.9	103.4	107.6	100.2	90.5	88.8	99.8	99.8	95.3	98.7	5.7	5.8	13.8	Pass	98.7	Pass
214.0	B-106	MND/45/Com.P/W/PG	100.2	96.1	97.1	97.6	97.6	95.7	100.1	107.2	97.4	97.1	98.6	3.3	3.4	8.0	Pass	98.6	Pass
215.0	B-107	MND/45/Com.P/W/PG	105.6	104.5	98.5	103.5	93.4	106.1	102.2	102.4	101.1	97.2	101.4	4.0	4.0	9.7	Pass	101.4	Pass
216.0	B-108	MND/45/Com.P/W/PG	86.8	99.3	100.8	92.0	96.0	98.8	97.8	93.3	97.2	97.5	95.9	4.2	4.4	12.6	Pass	95.9	Pass
222.0	PA-005	MM15/MND/01/W/PG	101.2	91.0	98.5	100.6	97.6	101.3	96.6	96.5	92.2	96.2	97.2	3.5	3.6	9.8	Pass	97.2	Pass
229.0	PA-013	5/MND/03/Com.P/PG	103.1	101.0	101.6	103.8	102.1	95.2	94.9	93.8	97.2	100.8	99.4	3.7	3.7	9.0	Pass	99.4	Pass
234.0	PB-005	M15/MND/02/Pre.H/PG	97.0	98.7	94.8	94.0	95.7	97.1	92.7	95.6	91.9	97.7	95.5	2.2	2.3	8.2	Pass	95.5	Pass

Appendix 15: Dissolution test results of pioglitazone HCl collected from Myanmar in 2015

1st stage



Kanazawa Univ. Dissolution test : Each unit is not less than Q+5% (Q=80%)

ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	Mean of % Quantity	SD of % Quantity	CV of % Quantity	Judge
1.0	A-001	15/MND/01/Com.P/PG	94.3	91.9	96.3	96.1	95.8	97.4	95.3	2.0	2.1	Pass
11.0	A-011	MM15/MND/04/W/PG	103.1	96.9	100.2	94.2	94.9	96.4	97.6	3.4	3.5	Pass
13.0	A-013	MND/05/Pri.H/PG	88.3	88.0	91.6	84.6	85.6	96.0	89.0	4.2	4.7	Pass
23.0	A-023	M15/MND/07/Pri.H/PG	100.5	101.0	97.5	99.6	96.9	97.3	98.8	1.8	1.8	Pass
31.0	A-031	MM15/MND/10/W/PG	101.1	94.4	97.8	99.6	98.8	98.2	98.3	2.2	2.3	Pass
32.0	A-032	MM15/MND/10/W/PG	69.2	53.3	63.5	70.8	70.9	74.6	67.0	7.6	11.4	Fail
40.0	A-040	5/MND/13/Com.P/PG	96.8	93.4	92.2	95.3	96.7	96.1	95.1	1.9	2.0	Pass
44.0	A-044	15/MND/14/Com.P/PG	93.9	93.6	91.7	95.9	85.9	96.0	92.8	3.7	4.0	Pass
49.0	A-049	5/MND/16/Com.P/PG	97.6	95.7	97.2	99.7	91.3	96.9	96.4	2.8	2.9	Pass
51.0	A-051	5/MND/18/Com.P/PG	108.7	95.4	97.9	93.4	98.5	87.5	96.9	7.0	7.2	Pass
59.0	A-059	MM15/MND/23/W/PG	96.7	95.3	89.7	93.5	92.6	101.3	94.8	4.0	4.2	Pass
62.0	A-062	MM15/MND/23/W/PG	54.9	71.2	70.9	72.9	76.0	80.8	71.1	8.7	12.3	Fail
64.0	A-064	MM15/MND/23/W/PG	86.9	85.4	84.5	88.1	88.3	88.1	86.9	1.6	1.9	Pass
66.0	A-066	15/MND/24/Com.P/PG	85.0	87.3	94.1	92.8	85.1	98.3	90.4	5.4	6.0	Pass
69.0	A-069	5/MND/25/Com.P/PG	95.5	99.6	102.9	97.2	92.2	97.0	97.4	3.6	3.7	Pass
71.0	A-071	5/MND/26/Com.P/PG	105.2	98.0	101.3	98.8	96.1	98.9	99.7	3.2	3.2	Pass
78.0	A-078	5/MND/29/Com.P/PG	102.7	99.4	101.4	100.1	97.1	97.7	99.7	2.1	2.1	Pass
79.0	A-079	5/MND/29/Com.P/PG	50.3	37.9	53.0	43.2	50.6	50.8	47.6	5.8	12.2	Fail
86.0	A-086	M15/MND/31/Pri.H/PG	70.4	70.4	69.4	71.5	76.4	74.9	72.2	2.8	3.9	Fail
87.0	A-087	M15/MND/31/Pri.H/PG	104.6	100.4	95.9	98.0	99.2	95.9	99.0	3.3	3.3	Pass
90.0	A-090	MM15/MND/33/W/PG	100.2	94.4	99.5	85.8	85.9	84.9	91.8	7.1	7.8	Pass

Kanazawa Univ. Dissolution test : Each unit is not less than Q+5% (Q=80%)

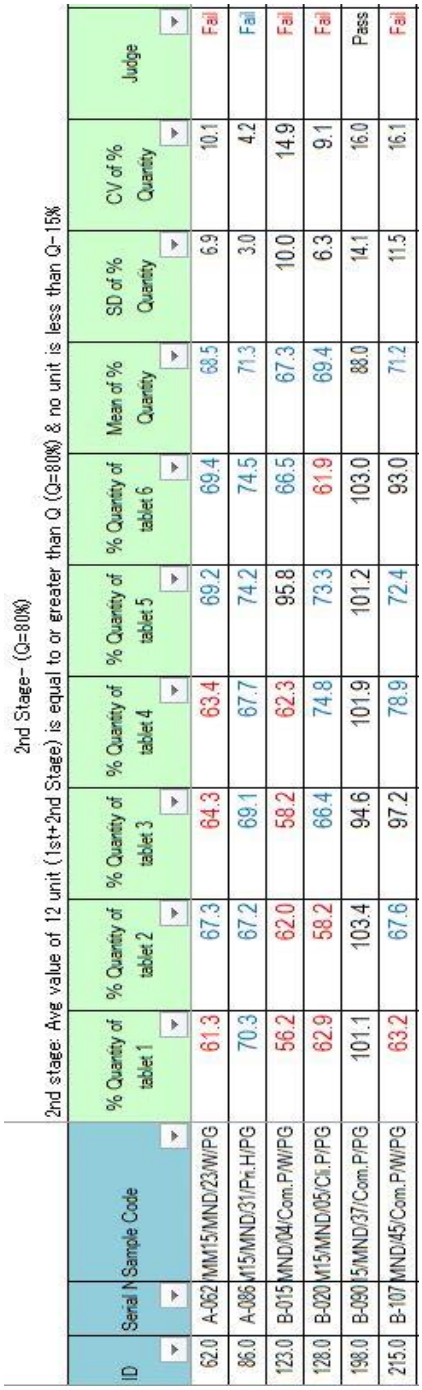
ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	Mean of % Quantity	SD of % Quantity	CV of % Quantity	Judge
101.0	A-101	5/MND/38/Com.P/PG	95.9	92.3	93.9	100.0	98.3	98.4	96.5	3.0	3.1	Pass
102.0	A-102	5/MND/39/Com.P/PG	102.4	99.0	101.6	93.6	91.8	100.2	98.1	4.4	4.5	Pass
103.0	A-103	/MM15/MND/40/W/PG	99.1	92.4	95.2	96.0	96.1	94.9	95.6	2.2	2.3	Pass
104.0	A-104	5/MND/41/Com.P/PG	98.0	103.6	94.8	101.0	94.9	103.4	99.3	4.0	4.0	Pass
105.0	A-105	5/MND/42/Com.P/PG	104.5	102.0	103.6	99.6	100.1	101.1	101.8	1.9	1.9	Pass
106.0	A-106	5/MND/43/Com.P/PG	90.4	97.8	101.6	94.6	99.1	95.1	96.4	3.9	4.1	Pass
108.0	A-108	M15/MND/44/Pre.H/PG	104.8	100.5	91.5	103.4	102.3	101.0	100.6	4.7	4.7	Pass
117.0	B-009	M15/MND/03/Pre.H/PG	102.3	98.1	100.7	96.1	100.1	98.8	99.3	2.2	2.2	Pass
121.0	B-013	MND/04/Com.P/W/PG	100.6	97.9	98.9	99.0	101.4	102.5	100.0	1.7	1.7	Pass
123.0	B-015	MND/04/Com.P/W/PG	67.9	64.1	66.7	67.0	71.0	70.2	67.8	2.5	3.7	Fail
128.0	B-020	M15/MND/05/Cli.P/PG	72.2	66.0	70.1	75.2	72.6	79.2	72.6	4.5	6.2	Fail
137.0	B-029	5/MND/08/Com.P/PG	99.1	98.8	101.2	98.3	105.2	97.1	99.9	2.9	2.9	Pass
141.0	B-033	5/MND/10/Com.P/PG	98.1	91.4	94.1	93.8	94.5	93.4	94.2	2.2	2.3	Pass
142.0	B-034	5/MND/10/Com.P/PG	102.5	97.7	102.6	103.7	102.2	102.4	101.9	2.1	2.1	Pass
143.0	B-035	5/MND/10/Com.P/PG	98.8	92.8	94.0	91.6	99.7	96.3	95.5	3.3	3.4	Pass
164.0	B-056	M15/MND/16/Pre.H/PG	101.2	88.3	88.6	89.0	90.2	85.1	90.4	5.6	6.2	Pass
169.0	B-061	5/MND/19/Com.P/PG	100.9	94.6	97.0	98.0	102.5	102.2	99.2	3.2	3.2	Pass
170.0	B-062	MND/20/Com.P/W/PG	97.8	100.4	100.4	100.3	99.8	100.2	99.8	1.0	1.0	Pass
172.0	B-064	5/MND/21/Com.P/PG	100.4	99.5	86.9	99.5	99.0	103.4	98.1	5.7	5.8	Pass
174.0	B-066	5/MND/22/Com.P/PG	88.5	94.8	94.2	98.2	98.9	92.7	94.5	3.8	4.0	Pass
175.0	B-067	5/MND/23/Com.P/PG	105.6	97.2	100.3	96.9	92.2	98.9	98.5	4.4	4.5	Pass

Kanazawa Univ. Dissolution test : Each unit is not less than Q+5% (Q=80%)

ID	Serial No .	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	Mean of % Quantity	SD of % Quantity	CV of % Quantity	Judge
177.0	B-069	M15/MND/25/Pre.H/PG	96.6	89.9	97.1	99.4	89.9	99.2	95.4	4.4	4.6	Pass
184.0	B-076	5/MND/29/Com.P/PG	90.8	97.9	100.7	91.4	101.2	94.9	96.1	4.5	4.7	Pass
186.0	B-078	5/MND/30/Com.P/PG	88.4	89.4	86.2	86.2	97.0	101.7	91.5	6.4	7.0	Pass
188.0	B-080	MND/32/Com.P/W/PG	95.7	96.0	96.8	91.1	98.8	93.0	95.2	2.8	2.9	Pass
190.0	B-082	5/MND/33/Com.P/PG	103.9	90.4	89.3	88.8	92.4	88.8	92.3	5.9	6.4	Pass
197.0	B-089	5/MND/36/Com.P/PG	95.4	90.6	98.0	94.9	87.0	94.7	93.4	3.9	4.2	Pass
198.0	B-090	5/MND/37/Com.P/PG	79.1	69.7	71.1	82.2	70.7	78.0	75.1	5.3	7.0	Fail
201.0	B-093	5/MND/37/Com.P/PG	100.5	96.8	90.1	91.4	100.1	94.3	95.5	4.4	4.6	Pass
202.0	B-094	5/MND/38/Com.P/PG	97.4	93.4	95.9	98.5	97.7	93.5	96.1	2.2	2.3	Pass
204.0	B-096	5/MND/39/Com.P/PG	87.6	97.8	95.7	88.6	98.1	97.1	94.1	4.8	5.1	Pass
207.0	B-099	5/MND/41/Com.P/PG	95.3	89.9	96.1	97.3	97.3	87.4	93.9	4.2	4.5	Pass
213.0	B-105	5/MND/44/Com.P/PG	95.8	97.9	101.4	90.6	99.9	98.6	97.4	3.8	3.9	Pass
214.0	B-106	MND/45/Com.P/W/PG	103.5	104.4	97.8	100.2	99.7	103.8	101.6	2.7	2.6	Pass
215.0	B-107	MND/45/Com.P/W/PG	61.3	66.2	63.2	71.5	69.1	73.0	67.4	4.6	6.9	Fail
216.0	B-108	MND/45/Com.P/W/PG	96.0	93.7	96.2	89.8	93.3	89.8	93.1	2.8	3.0	Pass
222.0	PA-006	/MM15/MND/01/W/PG	94.7	100.6	93.6	97.8	97.1	106.2	98.3	4.6	4.6	Pass
229.0	PA-013	5/MND/03/Com.P/PG	68.2	59.9	67.7	62.0	59.7	54.5	62.0	5.2	8.4	Fail
234.0	PB-005	M15/MND/02/Pre.H/PG	99.4	94.8	93.1	95.8	85.5	91.9	93.4	4.6	5.0	Pass

Appendix 16: Dissolution test results of pioglitazone HCl collected from Myanmar in 2015

2nd and 3rd stage



2nd Stage- (Q=80%)

2nd stage: Avg value of 12 unit (1st+2nd Stage) is equal to or greater than Q (Q=80%) & no unit is less than Q-15%

ID	Serial N	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	Mean of % Quantity	SD of % Quantity	CV of % Quantity	Judge
62.0	A-062	MM15/MND/23/W/PG	61.3	67.3	64.3	63.4	69.2	69.4	68.5	6.9	10.1	Fail
86.0	A-086	M15/MND/31/Pn.H/PG	70.3	67.2	69.1	67.7	74.2	74.5	71.3	3.0	4.2	Fail
123.0	B-015	MND/04/Com.P/W/PG	56.2	62.0	58.2	62.3	95.8	66.5	67.3	10.0	14.9	Fail
128.0	B-020	M15/MND/05/Cli.P/PG	62.9	58.2	66.4	74.8	73.3	61.9	69.4	6.3	9.1	Fail
198.0	B-090	5/MND/37/Com.P/PG	101.1	103.4	94.6	101.9	101.2	103.0	88.0	14.1	16.0	Pass
215.0	B-107	MND/45/Com.P/W/PG	63.2	67.6	97.2	78.9	72.4	93.0	71.2	11.5	16.1	Fail

3rd Stage- (Q=80%)

alue of 24 units (1st+2nd+3rd Stage) is equal to or greater than Q(Q=80%), not more than 2 units are less than Q-15% & no unit is less than

ID	Serial No.	Sample Code	% Quantity of tablet 1	% Quantity of tablet 2	% Quantity of tablet 3	% Quantity of tablet 4	% Quantity of tablet 5	% Quantity of tablet 6	% Quantity of tablet 7	% Quantity of tablet 8	% Quantity of tablet 9	% Quantity of tablet 10	% Quantity of tablet 11	% Quantity of tablet 12	Mean of % Quantity	SD of % Quantity	CV of % Quantity	Judge	All Stage Final Judge
86.0	A-086	M15/MND/31/Pn.H/PG	72.9	72.5	57.4	74.3	76.9	73.7	68.7	81.3	77.6	73.6	79.3	78.4	72.6	5.0	6.8	Fail	Fail

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