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



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# 学位論文要旨

**Background**

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.

**Objectives**

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.

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

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. For this purpose we conducted pharmacopoeial quantity, content uniformity and dissolution tests of 156 samples of omeprazole capsules collected in Cambodia in 2010 and Myanmar in 2014 (Table 1). High failure rates were found, especially in dissolution testing, and detailed investigation of several unacceptable samples was carried out by means of in-vitro dissolution profiling, scanning electron microscopy (SEM) and X-ray computed tomography (X-ray CT) to identify the cause of failure.

Dissolution profiling with and without the acid stage showed that acid caused premature omeprazole release, indicating that the enteric coating of the omeprazole granules was ineffective. SEM examination of two failed samples revealed cracked and broken granules mixed with apparently intact omeprazole granules in the capsule. X-ray CT examination indicated that some granules of failed samples completely lacked enteric coating, and others had incomplete and non-uniform enteric coating or malformation.

In conclusion, omeprazole capsules collected in Myanmar and Cambodia showed high failure rates in pharmacopoeial tests, especially dissolution tests. Some samples were found to have ineffective or

absent enteric coating of the granules, resulting in premature dissolution and degradation in acidic conditions. This is a potentially serious public health issue that needs to be addressed by regulatory authorities in Cambodia and Myanmar, possibly through a collaborative initiative with manufacturers.

**Table 1: Outline of the samples and the summary of the quality test results for omeprazole collected in Cambodia 2010 and Myanmar 2014**

| Country | Shop category | No. of samples (n/%) | Country of manufacturer | | Quality tests | Acceptable n/% | Unacceptable n/% | Pending* n/% |
|---|---|---|---|---|---|---|---|---|
| | | | Domestic( n/%) | Imported (n/%) | | | | |
| Cambodia 2010 (n = 91) | Pharmacy | 26/28.5 | 2/2.2 | 89/97.8 | Quantity | 54/59.3 | 22/24.2 | 15/16.5 |
| | Depot | 45/49.5 | | | Content Uniformity | 31/34.1 | 14/15.4 | 46/50.5 |
| | Wholesaler | 8/8.8 | | | | | | |
| | Outlet | 12/13.2 | | | Dissolution | 42/46.2 | 45/49.4 | 4/4.4 |
| Myanmar 2014 (n = 65) | Pharmacy | 35/53.8 | 0/0 | 65/100 | Quantity | 42/64.6 | 23/35.4 | 0/0 |
| | Hospital | 26/40 | | | Content Uniformity | 56/86.2 | 9/13.8 | 0/0 |
| | Wholesaler | 4/6.2 | | | Dissolution | 48/73.8 | 17/26.2 | 0/0 |

*insufficient material available for full testing

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

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.

For this study we evaluated the quality of omeprazole purchased via the internet and personally imported into Japan. We also compared the quality of these samples with that of the same products from the same manufacturers previously collected in surveys in two other Asian countries.

The personally imported omeprazole samples, which originated from 17 different manufacturers in 6 countries, were evaluated by observation, authenticity investigation, and pharmacopoeial quality analysis. Among the 28 samples analyzed, 26 (92.9 %) have passed in quantity and content uniformity tests, and all the samples have passed in the dissolution test (Table 2). Dissolution profiling confirmed that all the personally imported omeprazole samples remained intact in the acid

stage. On the other hand, samples from some of the same manufacturers, previously collected during surveys in Cambodia and Myanmar, frequently showed premature omeprazole release in acid. Raman spectroscopy and principal component analysis (PCA) showed significant variation between omeprazole formulations in personally imported samples and the samples from Cambodia and Myanmar. Thus, our results indicate that omeprazole formulations distributed in different market segments by the same manufacturers were of diverse quality. Measures are needed to ensure consistent quality product, and to prevent entry of substandard products into the legitimate supply chain.

**Table 2: Quality test results of omeprazole personally imported into Japan**

| Test | Quantity | | Content Uniformity | | Dissolution | |
|---|---|---|---|---|---|---|
| **Judge** | Pass (%) | Fail (%) | Pass (%) | Fail (%) | Pass (%) | Fail (%) |
| **No. of samples (%)** | 26 (92.9) | 2 (7.1) | 26 (92.9) | 1 (3.6)* | 28 (100) | 0 |

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

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.

Between 2012 and 2015 a cross-sectional investigation was conducted to study the quality of pioglitazone. 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 3.

Collected samples were then analyzed by visual inspection, authenticity investigation, and pharmacopoeial analysis by high-performance liquid chromatography. Although no packaging defect or suspicious information was found from the visual inspection, minimum response was found from the manufacturer during authenticity investigation.

After the final assessment, quality test results of the sample from Shanghai were 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. In Myanmar 2015, among the collected 60 samples 13.3% samples were found to be failed. 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%. 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.

**Table 3: Outline of the samples by sampling site, category and strength**

| Sampling Site | Year | Category | Strength | | | |
|---|---|---|---|---|---|---|
| | | | 15 mg | 30 mg | 45 mg | |
| **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 | | | |

**The health consequences of falsified medicines: A study of the published literature**

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.

For this study we searched PubMed for articles dealing with the health cost of falsified medicines, focusing on their consequences for mortality and morbidity, as well as the scale of the issue, the

geographic extent, the medicines affected, and the harm caused, using pre-optimized keywords "(counterfeit OR fake OR bogus OR falsified OR spurious) AND (medicine OR drug)".Searches up to February 2017 yielded 2006 hits, of which 1791 were full-length articles in English. Among them, we found 81 papers that qualitatively or quantitatively described 48 incidents in which falsified medicines caused patients to suffer serious adverse effects, injury, symptoms or death.

The distribution of incidents were examined according to the economic status of the countries involved, regional location in the world, therapeutic category of the medicines, number of incidents by year, number of victims by year, and characteristics of the falsified medicines. Among the 48 reported incidents, 27 (56.3%) occurred in developing countries and 21 (43.7%) in developed countries. Theseincidents involved a total of 7200 casualties including 3604 deaths(death rate 50.1%).

The results indicate that all types of medications have been targeted for falsification, and falsified medicines have had a serious impact on the health of both adults and children worldwide, with similar numbers of incidents in developing and developed countries.

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.

# 審査結果の要旨

Rahman 氏の業績の第一は、カンボジア、ミャンマーの市中薬局で販売されているプロトンポンプ阻害薬オメプラゾールカプセルが、甚だしい溶出性不良、特に、耐酸性不良を示す原因を突き止めたことである。カプセル中の顆粒の電顕観察では、溶出性の優れた製品に比べ不良製品では表面構造が粗く亀裂が認められること、Ｘ線ＣＴからは、溶出性不良製品には耐酸性被膜が欠如、または破損していることを認めた。すなわち、顆粒の耐酸性被膜が欠如または不完全なものが使用されていることを明らかにした。製品により顆粒の色や有効成分含量にも差があり、起源の異なる複数顆粒の混合も示唆された。業績の第二は、溶出性不良製品が日本にも個人輸入されているかカンボジア、ミャンマーの同一製品と比較したことである。Ｘ社の製品について、個人輸入品は局方試験で合格、カンボジア、ミャンマー製品は不合格であった。携帯ラマン分光分析及びＰＣＡ分析から、個人輸入製品はカンボジア、ミャンマー製品とは異なる製品であり、カンボジア、ミャンマー製品間も近似しているが同一ではないことが明らかになった。すなわち、Ｘ社は仕向け地により、同一製品であっても異なる基準で作成していた。第三に糖尿病治療薬ピオグリタゾン錠の個人輸入、中国、ミャンマー収集サンプルにおいても溶出性不良が認められ、溶出性不良はユニバーサルな問題と考えられた。第四に PubMed 収載論文の調査により、偽造医薬品が原因で、7,306 名に健康被害が発生しうち 3,710 名 51%が死亡していることを明らかにした。以上、これまで知られていなかった不良薬、偽造医薬品の製剤化不良問題や健康影響を明らかにしたもので、本審査委員会は, 審査員全員一致で, Rahman Mohammad Sofiqur 氏に対して博士（学術）の学位を授与することが適当であると判断した.