Journal of Food and Drug Analysis

Volume 20 | Issue 1 Article 9

2012

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Recommended Citation

Yang, H.-L.; Shen, L.-J.; Huang, C.-F.; Lin, C.-Y.; Chen, W.-H.; Hsieh, Y.-T.; and Wu, F.-L.L. (2012) "Are brand-name drugs of better quality than generics? Research at a Medical Center in Taiwan," *Journal of Food and Drug Analysis*: Vol. 20 : Iss. 1 , Article 9.
Available at: https://doi.org/10.38212/2224-6614.2066

Journal of Food and Drug Analysis, Vol. 20, No. 1, 2012, Pages 6-11 藥物食品分析 第二十卷 第一期

Are Brand-Name Drugs of Better Quality than Generics? Research at a Medical Center in Taiwan

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(Received: January 7, 2011; Accepted: August 26, 2011)

ABSTRACT

Medical institutions usually ensure the quality of medications by reviewing manufacturing documents and examining the appearance of the drugs. However, these mechanisms may not be robust enough to confirm the quality of the medications used. To evaluate the quality of medicines used at a medical center in Taiwan, a total of 190 new or formulary drugs were analyzed in a period from April 2004 to June 2010. For each medication, at least one test in the pharmacopeia or pharmaceutical manufacturers' specifications was chosen according to the dosage form or clinical requirement. A total of 437 tests were conducted. The overall failure rate was 5.8% (11/190) among all the drug products tested. Higher failure rates were seen in drugs with special dosage forms (12.5%) or dubious quality (7.7%). Although the failure rates of domestic brand-name drugs (9.1%, 2/22) and imported generic drugs (16.7%, 1/6) appeared to be higher than those of imported brand-name drugs (0%, 0/29) and domestic generic drugs (6.0%, 8/133), there was no significant difference among the various groups by Fisher's exact test due to the small sample size. Nevertheless, this study shows that there are still some substandard medicines in the market. The quality of imported brand-name drugs was shown to be unquestionable. The quality of domestic generic drugs was found to be equivalent to that of domestic brand-name or imported generic drugs. In-house laboratory analysis is an effective method that can be used together with the review of manufacturing documents to ensure the quality of drugs used at health-care institutions.

Key words: brand-name drugs, generic drugs, analysis, quality control

INTRODUCTION

The effectiveness of pharmacotherapy depends not only on the accuracy of the prescription, the dispensing process and the administration process, but also on the quality of the drug itself[(1)]. According to the World Health Organization (WHO)[(2)], the term "poor-quality medicine" can be two-fold: one being counterfeit medicine and the other being substandard medicine. Counterfeit medicine is illegal; it may not contain the main component, contain less than the labeled amount, or contain other unlabeled components. Substandard medicines are legal drugs containing the correct main component, but either the specification is inconsistent with the standard or the amount is insufficient or excessive. In other cases, the amount of the active ingredient may be ample, but the overall compound may be ineffective due to poor formulation, part of the analytical process, or dissolution properties. Without laboratory analysis, health authorities, hospitals and patients cannot differentiate substandard medicines.

Medications in Taiwan can be obtained from different sources. There are imported brands, domestic manufactured brands, imported generics and domestic generics. These are all under the supervision of the Taiwan Food and Drug Administration (TFDA)[(3)]. The TFDA and health bureaus of local governments have mechanisms of random inspections and analysis to ensure the quality of marketed drugs[(4,5)]. In 1977, there were more than 600 pharmaceutical manufacturers in Taiwan. After the promotion of Good

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Manufacturing Practice (GMP) and cGMP by the Department of Health (DOH), only 163 manufactures remained in 2005. To ensure that pharmaceutical products made in Taiwan meet the international standards, the DOH made an announcement on December 18, 2007 that drug manufacturers should comply with PIC/S (Pharmaceutical Inspection Co-operation Scheme) GMP. In July 2010, 12 domestic drug manufacturers passed the requirements of the PIC/S GMP in Taiwan. The Bureau of National Health Insurance (NHI) also raised reimbursement prices for medications made by these certified pharmaceutical manufacturers[6].

Within a medical institution, such as a hospital, counterfeit medicine is not a typical problem, as the Pharmacy and Therapeutic (P&T) Committee has to ensure the quality of medications for patients[7-9]. At our medical center, when a drug formulary application is filed, the pharmacy department has to review the specifications, and certificates of analysis (CCA) of the end product and its raw materials. For domestic generic manufacturers with whom we have no prior business relationship, the P&T Committee has to inspect the plant. In addition to the review of manufacturing documents and examination of the appearance of the medication, spot checks and in-house laboratory analyses are conducted on a routine basis to ensure the quality of medicines used in our hospital. To evaluate the quality of medicines used in medical institutions, a retrospective analysis of the quality control data obtained during the period from April 2004 to June 2010 at our medical center was performed.

MATERIALS AND METHODS

I. *Criteria for Drug Analysis*

In the National Taiwan University Hospital, drug analyses are performed in the following circumstances: (1) routine analysis of the drugs available at the hospital, (2) product switch due to annual bidding, (3) drugs with narrow therapeutic ranges, such as digoxin, phenytoin and warfarin, (4) drugs with special dosage forms, such as extended-release or enteric coated formulations, (5) drug complaints from health professionals or patients, (6) substitutes for a discontinued drug, and (7) drugs under formulary review. Analyses performed in situations 1 through 5 are for existing formulary drugs, whereas situations 6 and 7 are for new drugs. When a formulary drug fails the analysis, the Department of Pharmacy would ask for a recall. After an improvement is made by the manufacturer, three consecutive batches of the drug would be analyzed to ensure that the quality is consistent. If the manufacturer fails to improve the quality of the drug, the hospital would either discontinue the medication or switch brands. A medication under formulary evaluation that fails the analyses would be rejected by the P&T Committee.

II. *Methods and Test Items for Drug Analysis*

Samples were collected from more than one batch for each drug. Medications that were listed in a pharmacopeia were analyzed according to the criteria and methods specified in various pharmacopeias with editions published within the last 5 years[10-13]. Medications that were not listed in any pharmacopeia, for example, drugs that still had a patent or drugs that were rarely used, were analyzed according to the specifications provided by the manufacturers. Different items in the specifications were chosen for analysis according to the purpose of use or dosage form. The tests used for different dosage forms are listed in Table 1.

For routine analysis, usually only one test item in the pharmacopeia was performed. For drugs under formulary review, the specifications and certificates of analysis of the products were reviewed, and all the test items listed in the pharmacopeia or manufacturers' specifications were performed, if all the required instruments and facilities were available. Table 2 shows the instruments utilized for quality control.

Any single analytical result that failed to meet the specification of the pharmacopeias or manufacturers would result in the listing of a drug as a failure drug, regardless of the number of test items performed.

III. *Interpretation of Results*

Whether a drug passed a test was based on the specifications in a particular pharmacopeia or provided by the manufacturer. Using the assay test as an example, the active ingredient of most products should be within 90 to 110% of the labeled amount, unless otherwise specified. If the result was out of this range, it would not be acceptable. When a drug failed any single test, it would be categorized as substandard.

IV. *Statistical Analysis*

Fisher's exact test with the SPSS 11.5.0 (SPSS Inc., Chicago, IL, USA) software was used to test the differences in failure rates among various groups. A p value of less than 0.05 was considered statistically significant.

Table 1. Tests performed for different dosage forms

Test	Oral preparations		Injection
	Solid	Solution	
Identification	✓	✓#	✓#
Assay	✓	✓#	✓#
Dissolution test	✓#		
Disintegration test	✓		
Friability test	✓		
Uniformity of dosage units	✓	✓	✓
pH		✓	✓#
Sterility			✓

The most frequently performed test(s) for a specific dosage form.

Table 2. The instruments used for quality control at the medical center

Instrument	Brand	Model	Applications
Ultra Performance Liquid Chromatography (UPLC)	Waters (Massachusetts, USA)	ACQUITY UPLC® System with Photodiode Array Detector	Quantitative analysis [a] / Qualitative analysis [b]
High Performance Liquid Chromatography (HPLC)	Agilent (California, USA)	Quaternary pump: GA1311A Autosampler: G1329A Vacuum degasser: G1322A Thermostat for sample: G1330A Thermostatted column compartment: G1316A DAD detectors: G1315B Fluorescence detectors: G1321A	Quantitative analysis [a] / Qualitative analysis [b]
UV-visible spectrophotometer	Agilent (California, USA)	Agilent 8453 spectrophotometer	Quantitative analysis [a] / Qualitative analysis [b]
pH meter	Radiometer (Lyon, France)	PHM210	pH determination
Disintegration tester	Shin Kwang (Taipei, Taiwan)	CT-1, product number: SK-30201	Disintegration test
Friability tester	Betatek Inc. (Toronto, Canada)	Electrolab Friabilator Model EF-1W	Friability test
Dissolution tester	VanKel (California, USA)	VK7010 with Cary 50 UV-Vis spectrophotometer	Dissolution test
Electronic analytical balance	Mettler Toledo (California, USA)	AG285 / PG5002-S	Weighing

[a] Quantitative analysis included tests for assay, dissolution and uniformity of dosage forms.
[b] Qualitative analysis included the identification test.

Table 3. Number of drugs tested and assays according to the reasons for drug analysis

Reasons for analysis	No. of drugs tested	No. of assays
Formulary drugs	(148)*	(289)
Routine spot-check	108	199
Product switch due to annual bidding	24	28
Drugs with narrow therapeutic ranges	11	26
Special dosage forms	8	13
Drugs of dubious quality	13	23
Drugs under formulary review	(56)*	(148)
Substitutes for discontinued drugs	39	104
Drugs under formulary application review	17	44
Total	(190)*	(437)

* A drug might be tested for more than one reason as shown in the table, but it was only counted once in the total number of drugs tested.

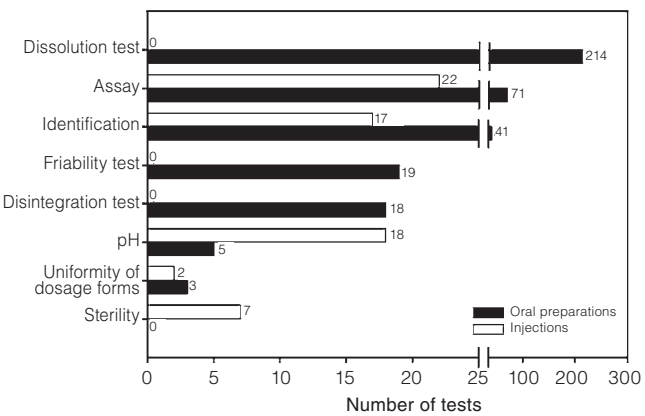

Figure 1. Quality control tests performed during the period from April 2004 to June 2010 at the medical center.

RESULTS

I. *Reasons for Drug Analyses*

During the study period, 437 tests were performed on 190 drug products (Table 3). Two hundred and eighty-nine (66.1%) tests were performed on 148 formulary drugs. Most of these tests were routine spot-checks for formulary drugs. Approximately 70% of the new drugs being tested were substitutes for discontinued medications. The average numbers of tests done were 1.95 per drug for formulary drugs and 2.64 per drug for new drugs.

II. *Quality Control Tests*

Eight different quality control tests were performed in the laboratory (Figure 1). About 84.7% (370) of the tests were done on oral medications (either solid or liquid dosage forms),

and the remaining were done on injections. The dissolution test was the most frequently performed test for tablets and capsules, followed by assay and identification. Assay, pH and identification were the tests most frequently performed on injections. More than 73% of the analyses were performed on generic medications, especially domestic generic medications (70.0%) (Table 4).

III. *Failure Rate*

Out of 437 tests on 190 drugs, 25 tests on 11 drugs failed, yielding a failure rate of 5.8% in terms of the number of drugs tested. Ten out of the 11 drugs that failed the analyses were made in Taiwan (either generic or brand-name drugs); the other one was a generic imported from Japan, which failed both assay and dissolution tests. Although generic drugs accounted for 73.2% of the drugs being analyzed, they accounted for 81.8% of the drugs that failed the tests (Table 4). No imported brand-name medicine failed the analyses. The failure rates of imported generic drugs (16.7%, 1/6) and domestic manufactured brand-name drugs (9.1%, 2/22) were higher than those of imported brand-name drugs (0%, 0/29), but the difference was not statistically significant ($p > 0.05$).

The failure rates varied significantly when categorized by reasons for analyses (Figure 2). The highest failure rate was found for drugs that were analyzed due to special dosage forms (12.5%), followed by drugs of dubious quality (7.7%) and drugs under review by the P&T Committee (5.9%). On the contrary, no failure was observed in drugs with narrow therapeutic ranges or brand switching due to annual bidding.

DISCUSSION

I. *Active Analyses to Ensure Drug Quality*

We have taken the initiative to actively analyze drugs in use or under evaluation at the medical center. Around 15% of the formulary drugs had been analyzed during routine spot checks. These include mainly generic drugs (73.2%), especially domestic generics. The average numbers of tests performed were 1.95 per drug for formulary drugs and 2.64 per drug for new drugs. Overall, 5.8% of the drugs sampled

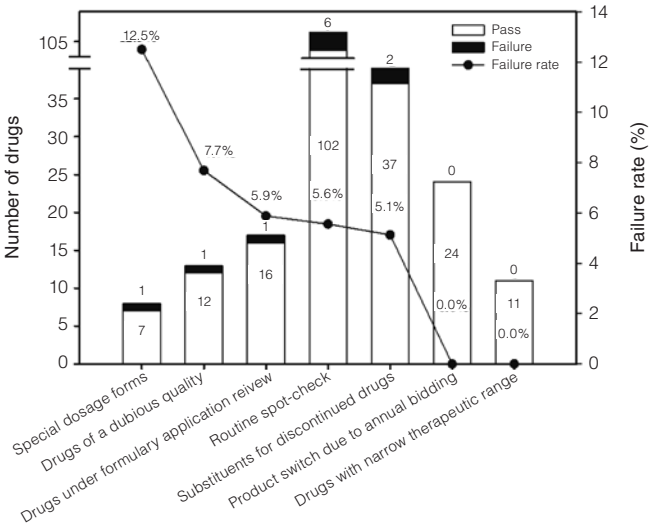

Figure 2. Failure rate of the drugs in accordance with the reasons for testing.

Table 4. Failure rate of drugs from different sources*

Failure rate analysis / Drug categories	Drugs available in different categories[a] (n ≅ 1250)	Sampling rate of each category[b]	Distribution of tested drugs in different categories[c] (n = 190)	Distribution of failed drugs in different categories[d] (n = 11)	Failure rate of each category[e]
Brand-name drugs	49.9%	5.6%	26.8%	18.2%	3.9% (2/51)
Imported	45.0%	5.1%	15.2%	0%	0% (0/29)
Domestic	4.9%	9.7%	11.6%	18.2%	9.1% (2/22)
Generic drugs	50.1%	24.6%	73.2%	81.8%	6.5% (9/139)
Imported	20.4%	8.6%	3.2%	9.1%	16.7% (1/6)
Domestic	29.7%	35.7%	70.0%	72.7%	6.0% (8/133)
Overall		15.0%			5.8% (11/190)

* There was no statistical difference in the failure rates among various categories by Fisher's exact test ($p > 0.05$).

[a] Drugs available in different categories is calculated by dividing the number of drugs in each category by the total number of formulary drugs (n ≅ 1250) in the medical center.

[b] Sampling rate is presented as the percentage of the drugs being tested among all the drugs in the same category.

[c] Distribution of tested drugs in different categories is calculated by dividing the number of tested drugs in each category by the total number of drugs tested (n = 190) in this study.

[d] Distribution of failed drugs in different categories is calculated by dividing the number of failed drugs in each category by the total number of failed drugs (n = 11) in this study.

[e] Failure rate is presented as the percentage of the failed drugs among all the drugs tested in the same category.

failed the analyses. No failure was found among imported brand-name drugs. Although the failure rate of domestic generic drugs (6.0%) was lower than that of imported generics (16.7%) or domestic brand-name drugs (9.1%), the difference among the groups was not statistically significant. The higher failure rate of domestic brands or imported generics may be due to the limited number of samples.

The Bureau of NHI in Taiwan reduces the reimbursement prices of drugs every year. This is one of the reasons for the withdrawal of many imported brand-name drugs from the market, increasing the chances that a given hospital searches for a substitute of the discontinued medication. Generic substitution is often required. In this study, the failure rates of brand-name and generic drugs were 3.9% and 6.5%, respectively, which was not statistically significant, due to the small sample sizes. No imported brand-name drugs failed any test in this study. However, a failure rate of 9.1% was observed when the production of a particular drug was shifted to a domestic original equipment manufacturer (OEM). The role of in-house quality control cannot be overlooked.

II. *Selection of Appropriate Tests*

In this study, the dissolution test was the most frequently used test to investigate oral solid dosage forms (immediate-release or extended-release). Once a drug passed the dissolution test at any designated time-point, that is, the dissolved amount of active ingredient was within the specifications, it could be assumed that the content of active ingredient also met the requirements of the assay test. On the contrary, if a drug passed the assay test, but failed the dissolution test due to formulation problems or variability in manufacturing processes, clinical effectiveness was doubtful[14-16].

Dissolution, assay and identification were the tests that were most frequently used (Figure 1). Their failure rates were 9.35% (20/214), 4.30% (4/93) and 0% (0/58), respectively. One failure (5.26%) occurred among 19 friability tests. No failure was found in other methods. This may be due to the limited number of tests performed.

III. *Prioritizing Drugs to be Analyzed*

In this study, drugs with special dosage forms or whose quality had been questioned had the highest failure rates, 12.5% and 7.7%, respectively. This indicated that more attention should be paid in these situations. Drugs with narrow therapeutic ranges should be closely monitored for clinical responses[17-19]. A minor change in its formulation or brand may cause the bioavailability, effects and toxicities to vary. However, none of the drugs with narrow therapeutic ranges failed the tests in this study. Four out of 11 drugs in this category were made in Taiwan. Although the results of this study may be limited by the retrospective nature of analysis and possible selection bias, the study did reveal the importance of in-house quality control of drugs, which is not currently available in the majority of hospitals.

This study revealed that there are still some substandard medicines in the market. Although the failure rate of domestic generic drugs was lower than that of domestic brand-name and imported generic drugs in our study, the difference was not statistically significant. In-house laboratory analyses are required to ensure the quality of drugs used in healthcare institutions. Special attention should be paid to drugs with special dosage forms or when the quality of the drugs is questionable.

ACKNOWLEDGMENTS

This study was supported by the Research Grant DOH99-TD-B-111-001 from the Department of Health of Taiwan.

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