

## CHAPTER 1

### INTRODUCTION

Drug products in the market, which contain the same active ingredients can be classified into two groups: generic and original (innovator) drug products. In Thailand, it is estimated that the consumption of medications is as high as 25-80 billion baht per year. The consumption of innovator drug products is one third of the total drug products consumption. In general, generic drug products are less expensive than their innovator counterparts because generic drug products do not have to duplicate the cost of research and marketing conducted by the original manufacturers. The difference of the prices of generic and innovator drug products in Thailand is very high. The generic substitutions in hospitals cause substantial decrease in annual drug expenditures of 216.6 million baht (Tantivess *et al.*, 2002).

When generic products become available, the market competition often leads to substantially lower prices for both the original brand name products and the generic one. In order to assure the therapeutic equivalence of these generic products, bioequivalence study needs to be investigated to provides important information in the overall set of data that ensures the safe and efficacious medicine that can be used interchangeably without significant therapeutic differences.

Bioequivalence study is basically a comparative bioavailability of drug in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Chen *et al.*, 2001). Thus two products are bioequivalent if their rate and extents of absorption are the same. The generic substitution can minimize the burden of patients who have to pay their own medications when they are sick. Generic drugs not only help saving the health care budget but also strengthening the health care system of the country.

Quetiapine is an atypical antipsychotic drug, it is an antagonist at multiple neurotransmitter receptors, including 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, D<sub>1</sub> and D<sub>2</sub>, histamine

(H<sub>1</sub>) receptor, alpha-1 and alpha-2 adrenergic receptors (Goren and Levin, 1998; Cutler *et al.*, 2002; Moor and Jefferson, 2004). Quetiapine has markedly improved the quality of life in many schizophrenic patients and has consequently become a first line antipsychotic (Sachse *et al.*, 2006).

Schizophrenia is the most common psychotic disorder that is among the world's top ten causes of long-term disability (Mueser and McGurk, 2004). It is a severe and chronic mental illness, associated with high prevalence about 0.5–1% of the population (Jablensky, 1997; Dargham and Laruelle, 2005). Almost 1% of people worldwide develop the disease during their lifetime and over 2 million persons are affected in the United States (Tomb, 1999). The incidence of schizophrenia is similar worldwide between 0.1 and 0.2 per 1,000 of the population. Schizophrenia affects men and women equally or slightly more common in male than in female. The age at onset of schizophrenia is gender related in some type of schizophrenia. The mean age for female patients is 25 years with a range of 15-30 years being the most common. For male patients, the mean age is 20 years with a range of 10-24 years (Ebert *et al.*, 2000).

Schizophrenia is a complex disorder comprised of different cluster of signs and symptoms. The features characteristic of schizophrenia is classified as positive, negative and disorganization symptoms (Koda-Kimble *et al.*, 2001). Positive symptoms include hallucinations (auditory, visual), delusions (perception, guilt, religion, mind control), thought disorders (tangentiality, derailment, circumstantiality), and bizarre behaviors (clothing, appearance, aggression, repetitive actions). Negative symptoms include social and emotion withdrawal, apathy, avolition, attention deficit, alogia, blunted affect, poor eye contact and poor insight and adjustment. Disorganization consists of incoherence, loose association, inappropriate affect and poverty of thought content. The mortality rate of schizophrenia is estimated to be twice that of the general population. Approximately 10% of the mortality is secondary to suicide. Young male schizophrenics are most likely to complete suicide attempts, especially early in their illness (Kay *et al.*, 2000). Schizophrenia is a very expansive illness because it usually affects people when they are young and it has a chronic course throughout the rest of their lives. Most people

with schizophrenia experience multiple hospitalizations and account for about 40% of hospital beds occupied (Goldman, 2000).

In Thailand, the Department of Mental Health, Ministry of Public Health reported that the incidence of schizophrenia is 293.2 cases per year per 100,000 of the population. Siriwanarangsun *et al.* (2004) studied the prevalence of mental disorder in Thailand in a national survey 2003, they found that the lifetime prevalence and point prevalence of schizophrenia are 1.17 and 0.59, respectively. Schizophrenia is the top twenty cause of year lived with disability (YLD). The disability adjusted life year (DALY) of schizophrenia in Thailand was 2%. This disease progressively impairs the personal, domestic, social and occupational ability of patients. This results in poor self-care, rejection by the family and society, unemployment and dependence on others (Kongsakon *et al.*, 2005).

Quetiapine was approved by the Food and Drug Administration (FDA) on September, 1997 (Timothy *et al.*, 2000). It is the most commonly prescribed antipsychotic drug in America and has been used by more than 19 million patients worldwide since its launch in 1997. It is effective in the treatment of mania and was approved in 2004 for this indication (Schatzberg, 2005). Its tolerability is higher than other classical antipsychotics. It causes a much lower incidence of extrapyramidal symptoms than that of haloperidol and it does not cause significant hematological changes such as agranulocytosis (Mandrioli *et al.*, 2002). This medicine not only helps people live longer, but also improves the quality of their lives because it is effective to reduce positive symptoms and also alleviate negative symptoms with low side effects.

Since quetiapine is commonly used for treatment of schizophrenia, several generic products are now being developed. Therefore, this study was aimed to investigate the bioequivalence between the generic drug, Quantia 200<sup>®</sup>, and innovator drug, Seroquel<sup>®</sup> in healthy Thai male volunteers. The results of this study would certainly provide necessary information for selecting and prescribing appropriate quetiapine formulation to ensure that the patients will receive a more cost-effective medication.