CHAPTER I

INTRODUCTION

The increase in the number of similar products from various sources has frequently placed people involved in the delivery of health care especially pharmacists in the position of having to select a product from among several apparently equivalent products — often of substitution of one product for another, whether it involved a brand-to-generic, generic-to-brand, or generic-to-generic change. Because of the increasing cost spiral of drug usage in most hospitals, pharmacists are put squarely in the middle. On one hand, they are sensitive to demands for a reduction in the cost of health care, but on the other hand he concerned about the quality of drug products that in some cases may be priced at a very small fraction of the cost of their trade name counterparts.

As with any decisions, the more data available the more comfortable one is in arriving at the final decision. The need to make these choices,in the light of the potential for *in vivo* inequivalency among products, has increased the demand for quantitative data on the clinical equivalence of similar drug products. Certainly, bioequivalency testing is an alternative solution to clinical testing for efficacy.

Ketoconazole is a synthetic imidazole antifungal drug, differing from earlier imidazole antifungals such as miconazole and clotrimazole in being effective, after an oral administration, against a wide variety of superficial or deep fungal infections (Heel et al., 1982). It has become a drug of choice for chronic mucocutaneous candidosis (American Society of Hospital pharmacist, 1989; Daneshmend and Warnock, 1988; Graybill and Craven, 1983; Hay, 1985; Hume and kerkering, 1983). In Thailand, ketoconazole is available for oral use as a 200 mg tablet and for topical use as 2% cream and shampoo (Jenny, 1989). At least fourteen brands of ketoconazole tablets are currently marketed, including an innovator's product (NIZORAL$^{(R)}$) with 1-2 times higher retail price than locally-made products (Jenny, 1989; Food and drug administration). Furthermore, two of locally-made products are film-coated tablets whose formulation and production processes may markedly affect bioavailability more than uncoated tablets (American Pharmaceutical Association, 1978).

Being a non-essential drug, ketoconazole could be selected from any of the fourteen brands by institutional practitioners (Public Health, Ministry) who must face with the cited problems because of no pertinent data on bioequivalence of this drug in Thailand. Besides it is well-documented that the differences in bioavailability do exist among chemical equivalent products and compliance

with official drug standards dose not necessarily guarantee bioequivalence (Cawthrone and Eckel, 1973).

Hence, the present study was conducted to assess the bioavailability of different brands of ketoconazole tablets commercially available in Thailand in order to facilitate drug product selection, in terms of the drug's efficacy and economic aspect, in health care settings.

Objectives

1. To compare the bioavailability of ketoconazole tablets commercially available in Thailand using the innovator's product as a reference for bioavailability comparisons.

2. To determine the *in vitro* quality of ketoconazole tablets marketed in Thailand such as disintegration time, dissolution rate constant in given media.

3. To investigate the correlations of *in vitro* parameters such as dissolution rate constant, disintegration time and principle pharmacokinetic parameters such as maximum plasma concentration, time to reach maximum plasma concentration and area under the plasma -concentration-time curve.

Significances of the Study

1. This study will provide bioavailability data of ketoconazole tablets that would be a useful information for any health care facilities in selecting the cheapest product which is bioequivalent to the innovator's product.

2. This study will provide some pharmaceutic factors affecting ketoconazole tablet bioavailability that may be used to predict the *in vivo* bioavailability of the tablets.

3. This study will provide the pharmacokinetics of ketoconazole following an oral administration in Thai healthy male volunteers, which would be a useful data for determining the optimum dosage regimens in certain patients.