1.0 INTRODUCTION

The anticonvulsant properties of valproic acid were first recognized in 1963, while this agent was being used as a solvent for other compounds. The sodium salt was introduced as an antiepileptic drug in 1967 and came on to the UK market in 1974.

Sodium valproate is especially valuable for the treatment of primary-generalized seizures. In controlled trials valproate has been proved to be as effective (80-90% seizure control) as carbamazepine and or phenytoin in the treatment of primary generalized tonic-clonic convulsions. (Shakir RA et al 1981; Wilder BJ et al 1983; Callaghan N et al 1985)

Sodium valproate comes under the category of narrow therapeutic index drugs under section 320.33(c) of Code of Federal Register 21 USA. The US FDA defines a product as having narrow therapeutic ratio as follows (CDER):

a. There is less than a 2 fold difference in median lethal dose and median effective dose values, or
b. There is less than 2 fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and

c. Safe and effective use of the drug requires careful titration and patient monitoring.

An updated definition was provided in the 2000 guidance, which defined narrow therapeutic range drug products as those "containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. (AMA annual featured report-Generic Drugs, 2002)

In a survey conducted in United Kingdom, increasing number of hospital pharmacists have been prescribing generic drug products. In most clinical conditions, this may be actually beneficial as there is no significant change in the quality of the patient care and it may be actually better as they may lead to significant cost saving. (Marriott JF 1999). However, there are clinical situations involving certain patients, disease states and
therapeutic agents, in which any change in drug plasma levels associated with brand substitution, might be of significant clinical importance. For those situations in which brand substitution is deemed undesirable, the clinical efficacy and/or toxicity profile of the agent concerned would be adversely affected by even small changes in drug concentration at the active site: any resultant adverse effect would also be of sufficient severity to warrant medical intervention. Consequently, therapeutic agents for which brand substitution should be avoided would be likely to exhibit one or more of the following characteristics: (Marriott JF1999)

- Narrow therapeutic index, which would manifest as a well defined, limited therapeutic concentration range (possibly necessitating blood level monitoring)
- Wide intra- or inter-patient variation in bioavailability (resulting from limited or erratic absorption).
- Drug pharmacokinetics that are highly dependent upon formulation
- Indicated for a critical purpose (patient condition and/or disease state)
- Extreme dosing accuracy indicated (by body weight or surface area)

In response to these recommendations, the British National Formulary (BNF) includes a special precaution attached to the entry for a number of drugs like Carbamazepine, Phenytoin, Sodium valproate, theophylline modified release, Aminophylline modified release, diltiazem long acting, nifedipine modified release, lithium, cyclosporin. (Marriott JF1999)

*These warnings indicate generally that brand substitution after dose stabilization might produce undesirable effects of some kind and should therefore be avoided.*

Borgheini G (2003) in his review summarized available data comparing the bioequivalence and therapeutic efficacy of brand-name psychoactive drugs with those of the corresponding generic products. These studies however few in number revealed differences in the efficacy and tolerability of brand-name and generic psychoactive drugs that had not been noted in the original bioequivalence studies. Specifically, one study found that plasma levels of phenytoin were 31% lower after a switch from a brand name to a generic product. Several controlled studies of carbamazepine showed a recurrence of convulsions after the shift to a generic formulation. (Welty TE et al 1992; Pedersen SA and Dam M 1985; Meyer MC et al 1992)
After a sudden recurrence of seizures when generic valproic acid was substituted for the brand-name product, an investigation by the US Food and Drug Administration found a difference in bioavailability between the two formulations. (Borgheini G 2003)

A recent case study in India has reported that when a generic sodium valproate was substituted by a branded formulation the frequency of the generalized seizures was reduced by 50%. (Dhanaraj M and Jayavelu A 2004). Therefore, there is a need to investigate the bioequivalence / non-equivalence of the marketed formulations of sodium valproate in India, in order to provide an insight to the prescriber about which brand of sodium valproate to prescribe and to the pharmacist about which brand to substitute in situations of non-availability.

The present study was therefore planned to investigate whether there is bioequivalence/ non-equivalence in the three-marketed brands of enteric-coated 500 mg tablets of sodium valproate in India.