Section 1: INTRODUCTION
INTRODUCTION

The Hydantoin class of compounds was discovered by Bayer in 1861. Most of these compounds have not been used clinically for a variety of reasons, primarily toxicity and relative ineffectiveness. But Phenytoin has been in widespread use for the better part of a century. Synthesized first by Blitz in 1908, it was tested first for hypnotic activity. Its anti-convulsant activity was recognized by Merrit and Puttman in 1938. Since then, it has been used to treat all varieties of epilepsy, except absence and myoclonic seizures.

Phenytoin has been classified as a drug with “high risk potential” (Doluisio et al, 1973) with respect to bioavailability problems. It has also been designated as a “Narrow Therapeutic Index” drug by the FDA. This implies that even small excursions above or below optimum plasma levels can cause toxicity or recurrence of seizures, respectively. Maintenance of a safe and effective plasma steady-state concentration requires that the absolute daily dose remain constant. Even minor alterations in the extent of absorption (bioavailability) can alter equilibrium substantially.

Further, Phenytoin is a drug subject to intense therapeutic monitoring. Therapeutic Drug Monitoring is done for drugs that lack correlation between dose and pharmacodynamic properties, for drugs that have nonlinear correlations between dose and effect, and for drugs that have a narrow therapeutic range (NTR) between the dose necessary to achieve beneficial effects and the dose that causes serious adverse effects when there is a direct concentration–effect relationship. Individualizing the drug dosage and the dosing interval can minimize the toxicity and maximize the therapeutic benefit of NTR drugs.

A number of reports of studies on the comparative oral bioavailability of Phenytoin following the 1968 Australian outbreak of Phenytoin intoxication have appeared in literature, which happened due to substitution in the marketplace of phenytoin formulation in which an excipient had been changed.

Problems related to differences in bioavailability between preparations of Phenytoin have been documented in Europe, North America and Australasia (Rambeck et al, 1977, Neuvonen b et al, 1979, Tsai² et al, 1992, Rosenbaum et al, 1994, Gogtay et al, 2003, to name a few). Further, the poor solubility of Phenytoin at physiological pH make it more prone to bioavailability problems. Also, the elimination kinetics of the molecule are such that relatively small bioavailability differences tend to produce surprisingly large changes in plasma drug concentrations and biological effects.
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Considering the above points, changing the brand of Phenytoin product on which a patient has been stabilized has been deemed unwise, unless the bioavailability and the pharmacokinetic parameters of each product is known to the fullest extent.

Many studies have shown differences in the rate and extent of absorption of Phenytoin between products. In spite of the awareness of the problems associated with the use of this molecule, reports of brands that fail to meet bioavailability standards still appear in literature. Reports of such studies conducted in India are relatively few in number (Gogtay et al, 2003). Often such reports have too low power to justify the results or an incorrect choice of innovator product has been made. This study is aimed and designed to correct such flaws.

In the treatment of epilepsy, it is vital that plasma drug concentration be maintained at an optimum level (10-20μg/ml) to prevent seizures. Therefore, the product must provide adequate drug levels not only at peak, but also trough points. This means that levels of Phenytoin have to be maintained at a desired level not only with an aim to prevent toxicity, but also to provide therapeutic benefit to the patient. Phenytoin, because of its poorly insoluble nature, non-linear pharmacokinetics and vulnerability to formulation characteristics like particle size, excipient etc, poses problems when it comes to fulfilling above-mentioned feature.

Generic versions of drugs have been mooted to be a good measure to reduce cost of therapy to the patient. Time and again, the concept of generic versions have come under attack from various sources because of suspected poor quality of the cheaper versions, more so in the case of narrow therapeutic index drugs. Many studies have been appearing in published literature for more than 50 years that seem to indicate that such fears may have a sound basis.

India is a country with not too stringent enforcement of regulatory laws for pharmaceuticals. It is home to an estimated 20,000 small and large-scale manufacturing units, many of them not following GMP laws appropriately and therefore, is a veritable store-house of poor quality drugs. In such a situation, a study is warranted that aims to test the quality of drugs in the Indian market. This study, therefore, has been designed to study the bioavailability of three different brands of phenytoin sodium in the Indian market and to compare the pharmacokinetic profile of these products in normal human volunteers.