"Medicine is a science of uncertainty and an art of probability" quoted by the famous Physician, Sir William Osler (1849-1919) gives the impulse on the fuss associated with the drug discovery and its consumption.

The current developments in the field of pharmaceuticals have dramatically changed the public health. Every new chemical entity has to pass through genotoxic tests in order to get regulatory approval. A negative on this crucial test takes the sample drug one step closer to the market. Genotoxic/carcinogenic potential has to be stated for numerous compounds which are often in pharmaceutical use. Independent and thorough testing is to be done for new compounds for which information is incomplete with respect to their interaction with macromolecules or that have the potential to generate reactive metabolite in the body.

Decades ago, chemical mutagenicity was central to drug discovery. However, intervening period saw chemical mutagenecity getting replaced by the term genetic toxicology. Presently genetic toxicology has become an important part of drug development. The aim of genotoxicity testing is to identify potentially hazardous drug candidates (Custer et al., 2008). History reveals that if a drug is not tested properly prior to marketing, it can have disastrous results. There has been lots of data regarding side effects of drugs leading to various chromosomal changes in animals and human beings. It is important for all drugs to undergo genotoxic testing before further development. This ensures that patients are not exposed to drug which causes side effects. Besides regulatory testing, genotoxicity assays are used to issue safety of recipients, metabolites, degradants etc.
Genotoxic effects are hardly assessable in an exposed population, but are generally considered serious, due to their unpredictable effects on subsequent generation especially due to the link between genotoxicity and cancer. In most of the developing countries including India, with poor economic conditions, the population has few trained medical personnel. Therefore, all medical ailments are not brought under direct medical supervision. As a result, a large percentage of the population resorts to self-medication with complete ignorance of the correct prescriptions. Further, the drugs are not strictly obtained by prescriptions, but are readily available as over-the-counter for the public.

The discovery of new drug needs a thorough investigation for its safety and efficacy before their release into the market (Purves et al., 1995). There are specific guidelines for testing of pharmaceuticals for genotoxicity. In India, Schedule 'Y' of Drugs and Cosmetic Rules 1988, Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services (DGHS), New Drugs Division issued by Ministry of Health and Family Welfare, Govt. of India, deals with the prerequisites to carry out the clinical trials of a new drug before its marketing, depending upon the status of the drugs in other countries. In United States the FDA's (Food and Drug Administration) Centre for Drugs and Biologics Evaluation and Research (CDER and CBER) recommend genotoxicity testing for all new drugs (Hutt et al., 1991). At present, the FDA accepts the three-test package as required by the Ministry of Health and Welfare (MHW) in Japan. In European Community (EC) mutagenicity data are required for the pharmaceuticals before the commencement of clinical trials and the marketing authorization (European Community Notes, 1987). The outcome of genotoxicity tests are needed for the design and conduct of long term Carcinogenicity study and interpretation of the test results (Alden, 1999). Genotoxicity has now became an ICH topic and the genotoxicity working group identified more than 60 strategic and technical issues, which differed
in substance between the regulatory authorities of the USA, the European Union and Japan. It was also noted that the importance given to various genotoxicity tests differed considerably from the guidelines of one country to another. (Christan, 1997; Alden, 1999; Shelby et al., 1991).

Doctors have relied primarily upon the Physicians’ Desk Reference (PDR) for the latest, most accurate drug information. Today that trusted knowledge is available through PDR health. The drug information on PDR health is written in lay man’s terms and is based on the FDA-approved drug information found in the PDR. It gives consumers explanations for the safe and effective use of prescription and non-prescription drugs. On the contrary, it is acknowledged that for many drugs in the PDR, additional unpublished information exists for both genotoxicity and carcinogenicity which led to discontinuation of the development of these drugs. Hence the PDR genotoxicity database is not representative of and cannot be used to draw inferences about the genotoxicity of the global chemical population (Synder and Green, 2001).

Genotoxicity testing of chemicals prior to commercialization is mandated by regulatory agencies worldwide. For the most part, a three to four-test battery including bacterial mutagenesis, in vitro mammalian mutagenesis, in vitro chromosome aberration analysis and an in vivo chromosome stability assay are required to assess the genotoxicity hazards (Synder and Green, 2001). Recent publications on new pharmaceuticals and new chemicals provide an interesting insight into how the individual assays performed by themselves and in combination in identifying genotoxic hazards (Broschinski et al., 1998; Muller and Kasper, 2000) can provide useful and vital information. The general conclusion is that (i) relatively few compounds were detected positive in vitro mutation induction assays in contrast to in vitro cytogenetic assays and (ii) a fairly large percentage of all regulatory submissions 25-30%, included positive results for at least one mutagenicity assay (Synder and Green, 2001).
From a drug development standpoint, it is important to have a thorough understanding of the mechanism of any 'positive' genetic toxicology findings so that informed decisions may be made with respect to risk. Further, in the requirements of most of the regulatory agencies, in vivo cytogenetic assays (micronucleus/chromosome aberrations/sister chromatid exchanges) are not made essential which is substituted by the equivalent in vitro assays. Consequently, adequate in vivo cytogenetic data are not available for many of the pharmaceuticals. However, the in vivo test is especially relevant to assess genotoxicity hazard because it allows consideration of factors of in vivo metabolism, pharmacokinetics and DNA-repair processes and is also useful in further investigation of a mutagenic effect detected by an in vitro genotoxicity test (Krishna and Hayashi, 2000).

Therefore, it is imperative that detailed investigations are carried out on the genotoxicity of marketed pharmaceuticals using multiple endpoints in different laboratories in a global basis. This will help formulation of regulatory policy guidelines as to ensure better public health, which is the ultimate objective of drug development. Recently, there is a growing concern about possible genotoxic and mutagenic potential of marketed pharmaceuticals in mammalian cells (Synder and Green, 2001; Donya, 2002; Perrone et al., 2002; Tunca et al., 2002).

However, from a detailed electronic search in the databases of Medline, PubMed and Toxline it has been found that not much independent investigations have been made on the genotoxicity of most of the marketed pharmaceuticals. In fact, for a quite significant number of pharmaceuticals, no genotoxicity data is at all available in the in vivo mammalian cytogenetic assays. In addition, considerable controversies exist among the genotoxicity reports arising out of different laboratories. Consequently, adequate in vivo cytogenetic data are not available for many of the pharmaceuticals.
For the genotoxic effects of physical and chemical agents, formation of chromosome aberrations is a cytogenetic endpoint (Masjedi et al., 2000). Micronucleus arises from chromosomal fragments or whole chromosomes which are not incorporated into daughter nuclei during mitosis (Countryman et al., 1976; Heddle et al., 1983). The micronucleus assay is a fast and sensitive cytogenetic technique for evaluation of chromosomal damage in human lymphocytes (Fenech et al., 1985; Fenech, 1997). Genotoxicity data of pharmaceuticals on germ line cells is extremely scanty. Chemically induced increase in sperm head damage is highly correlated to known germ cell mutagens; therefore more studies are required on the effect of pharmaceuticals in these cells (Wyrobek et al., 1975). Genetic alterations in germ cells may also lead to reproductive failure or genetic disorders in subsequent generations. Mutations in the germ line cells are the only cells capable of transferring it to the next generation, therefore more studies are required on the effect of pharmaceuticals in these cells. Further, the pharmaceutical agents may hyper sensitize the cells to another mutagen by way of altering its physiology and interaction with the cellular DNA.

Despite of these genotoxic tests guidelines the market is flooded with never ending list of genotoxic drugs available over the counter. Therefore, considering the context of the available literature, the objectives of the present study are as follows:

1. To study the genotoxic effects of selective pharmaceuticals, currently prescribed by physician, in the somatic cells of mammalian test system.

2. To evaluate the effect(s) of these pharmaceuticals in the male germ line cells.

3. Study on the effects of dietary antioxidants in modulating the possible genotoxicity potential of pharmaceuticals.

4. Study on the drug-mutagen interaction to evaluate the acquired susceptibility of few common pharmaceuticals.