"The task is not so much to see what no one yet has seen, but to think what no body yet has thought about that which everyone sees" quoted by the famous German Philosopher, Arthur Schopenhauer (1788-1860) gives the impetus to unfold our preconceptions with developed perception, common sense rounded out and being rigidly accurate in observation.

Human life has always entailed exposure to chemicals. The substances we eat, drink and breathe are composed of chemicals. Two major factors are responsible for the concern over genetic effects. The first is the concern for the protection of human gene pool. The second is connected with oncogenesis. The ultimate relationship between the tumorigenic and genotoxic properties of chemicals makes genetic testing mandatory for chemicals of unknown oncogenic potential. The twentieth century has seen substantial growth in the synthesis of new molecules, some of which have proved useful in treating disease, preserving food, and reducing the cost of commodities. In recent decades there has been widespread concern that synthetic chemical
substances – increasing in number and concentrations – and natural substances may adversely affect human health. In response to the concern, such agencies as the Environmental Protection Agency, the Consumer Product Safety Commission, the Occupational Safety and Health Administration, the Food and Drug Administration etc. began to monitor the use of chemicals world over. Recognition of the impact of these and other classes of substances on public health leads society to seek information for determining the magnitude of their potential effects. Such information is based primarily on predictions from results of toxicity studies (National Research Council Board, 1984). Another important factor in assessing the consequences of genetic effects is the location of the affected cell. If mutations occur in the cells, which are not part of the reproductive system (somatic cells), the resultant effect is only on the individual exposed to the genotoxic agent. However, if alteration occurs in gametes (sperm or ova) the change may affect subsequent generations (Brusick, 1980). The mutations induced in the gametes of an exposed individual may show expression immediately if it is dominant, or it may show expression after several generations if it is a recessive one.

The purpose of toxicity testing is to generate information about a substance’s toxic properties so that the health and environmental risks it poses can be adequately evaluated. Toxicity testing in laboratory animals provides many of the data needed for risk assessment, such as information on the possible effects of exposure to a substance and the exposure concentrations at which effects might be observed. The U.S. Environmental Protection Agency
(EPA) recognized the need for a comprehensive review of established and emerging toxicity-testing methods and strategies and the National Research Council (NRC) was entrusted to conduct such a review and to develop a long-range vision and strategy for toxicity testing. Toxicity-testing requirements to evaluate effects on human health often involve studies of whole animals, typically rats, mice, dogs, and rabbits, although other species, including humans, can be used. Exposures can range from short-term (an hour) to long-term (up to 2 years) and be continuous or episodic or consist of a single event. The objective of toxicity testing is to identify possible adverse effects of exposure to environmental agents, to develop dose-response relationships that can elucidate the severity of effects associated with known exposures, and ultimately to predict the effects of exposure of human populations. (BEST, 2006).

Over the last 50 years or so, 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).

We cannot deny the fact that the development of new drugs in the 20th century has dramatically changed the public health care and increased the average life expectancy considerably. At the same time, drugs have their own side effects. Therefore, the protection of the human gene pool and the integral relationship between mutagenicity and carcinogenicity are the two major factors which imparts vital importance to genotoxicity testing of chemicals of potential human exposure. It was Herman Druckrey, at a conference in Sweden, first used the word genotoxic for chemicals that can react with DNA, and thus have the potential of being mutagenic, cell transforming and carcinogenic (Weisburger, 1999). DNA repair can operate effectively and restore the integrity of DNA but only if this has a chance of operating prior to the synthesis of new DNA and mitosis, underwriting the importance of the rate of cell division (Weisburger, 1999).

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.).
al., 1998; Muller and Kasper, 2000) can provide useful and vital information. The general conclusion is that (i) relatively few compounds were detected as positive in the 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 cytogenetic endpoints in multiple 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 arise 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. Since mutations in the germ line cells are the only cells capable of transferring a mutation 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 even though it itself does not directly interact with the cellular DNA.

Therefore, considering the above mentioned facts and in the light of the available literature, the major objectives of the present study are as follows:

1. To study the genotoxic effects of some commonly prescribed marketed pharmaceuticals in the somatic cells of mammalian test systems in vivo.

2. To evaluate the effects of these pharmaceuticals in the male germ line cells.

3. To study the drug – mutagen interactions so as to evaluate the acquired susceptibility using the combined treatment with known mutagen.

4. To explore the possibility of using vitamin C to reduce drug – induced mutagenicity.