Nomination from FDA's Office of Orphan Product Development (OOPD)

p53 and TG.AC Alternative Cancer Studies on the Drug Pilocarpine

Pilocarpine is currently undergoing a chronic two year toxicity study that is supported by a sponsor who is considering developing Pilocarpine as an orphan product drug. In an effort to provide the FDA's OOPD and CDER with information on alternative testing protocols, to enhance the p53 and TG.AC database, and to validate these alternative test models for regulatory use, OOPD is requesting studies be conducted using NTP's p53 and TG.AC alternative cancer testing animal models.

Pilocarpine is currently approved for use by the FDA for treatment of symptoms of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck. It is a cholinergic papasympathominetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. There have been no long-term toxicity or carcinogenicity studies reported to FDA or in the literature. Pilocarpine has, however, been reported to be a reproductive and developmental toxin in rodents. Pilocarpine does not appear to be genotoxic in 1) Salmonella or E. coli assays, 2) *in vitro* chromosome aberration assays in CHO cell line, 3) *in vivo* chromosome aberration micronucelus test in mice, and 4) primary DNA damage assays (UDS) in rat hepatocyte culture cells.

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