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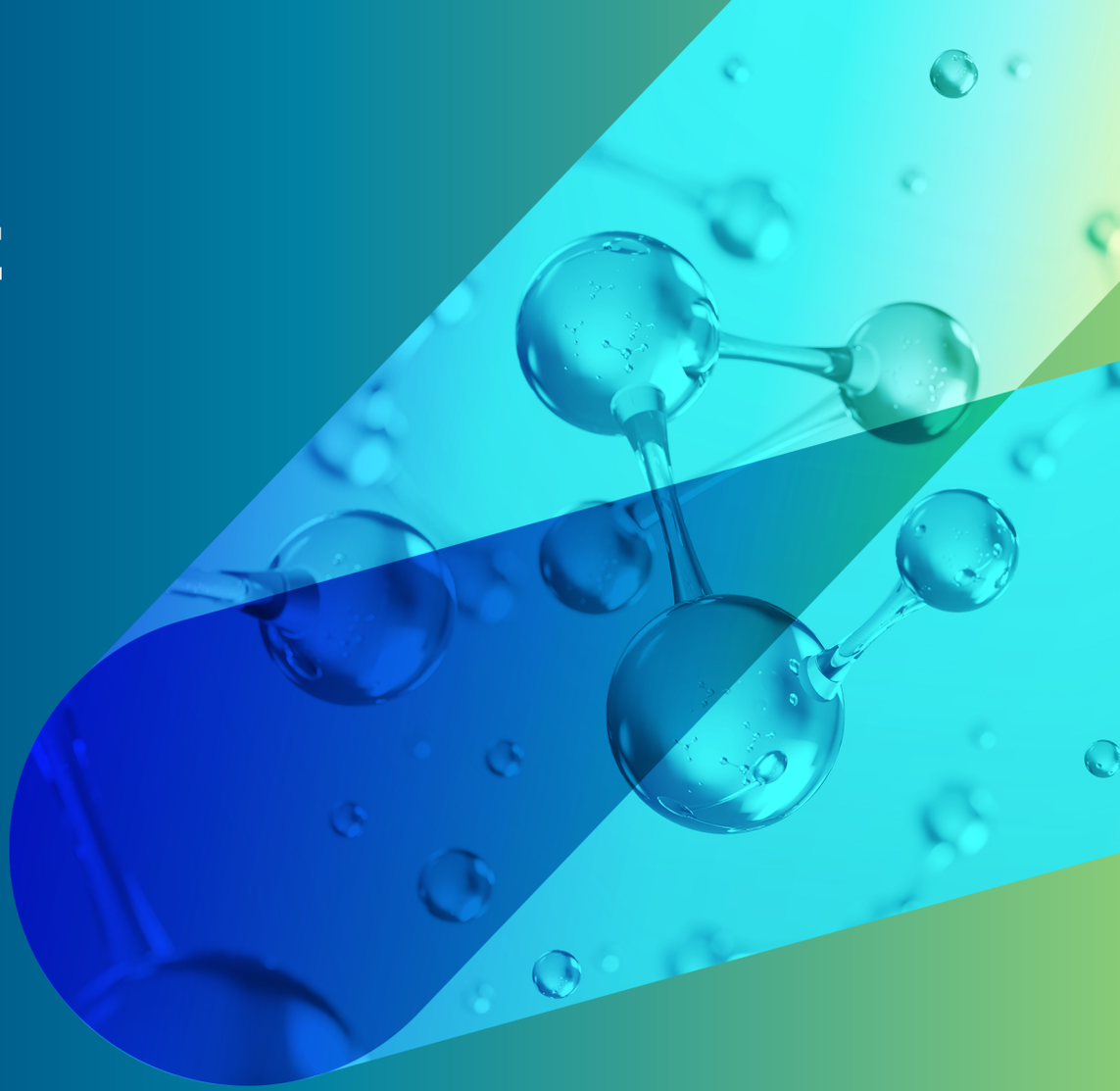

Enhanced AMES Test (EAT) for Nitrosamine Impurity Risk assessment

The robust control of genotoxic N-nitrosamine (NA) impurities is of prime consideration for the pharmaceutical industry.

In order to address sensitivity concerns surrounding the Ames test for Nitrosamine impurities, a new guidance has been published by regulatory authorities which recommends enhanced testing conditions for NDSRIs that are negative in the standard OECD-compliant assay, i.e., Enhanced Ames Test

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- APSL is delighted to support clients with Nitrosamine impurity profiling using 'Enhanced AMES Test' for the NDSRIs formed in their APIs or drug products, as a part of risk assessment proposed inrecent EMA and FDA regulations for marketing authorization of human medicinal products with N-nitrosamine impurities.
- We at APSL have well established procedures validated to conduct nitrosamine impurity profiling for NDSRI's complying with GLP standards to meet the requirements of regulatory agencies.
- APSL also has generated adequate negative control and N-Nitrosamine positive control response data to substantiate the testing of new NDSRIs from clients.
- APSL conducts EAT with petite turnaround time, complying to the checklist requirements recently published by EMA on 24 March 2024 in their recommendation to Appendix -3 of Q&A for marketing authorization of human medicinal products with N-Nitrosamine impurities.

Procedure:

- Briefly, Enhanced AMES Test (EAT) is conducted as bacterial reverse mutation test with inclusion of additional metabolic activation system using hamster liver S9 mix along with rat liver s9 mix during treatments using pre-incubation method for 3060- minutes, including recommended N-Nitrosamine positive controls like N-Nitrosodimethylamine (NDMA), 1-Cyclopentyl-4-nitrosopiperazine (CPP) and/or N-Nitroso propranolol (NNP) (guidance recommended NDSRIs) for the assay.
- EAT includes use of Salmonella typhimurium tester strains TA1537, TA1535, TA98, TA100 and Escherichia coli tester strain WP2 uvrA pKM101, treated in the absence of metabolic activation system and in the presence of 30% v/v rat and hamster S9 metabolic activation systems.
- Fold change in revertant colony counts over concurrent vehicle controls will be evaluated to derive the mutagenic potential of submitted NDSRIs.