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Is the genetic toxicology assessment of oligonucleotide therapies warranted?

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The European Federation of Pharmaceutical Industries and Associations (EFPIA)–Preclinical Development Expert Group (PDEG) established an Oligonucleotide Working Group (OWG) to review industry experience of developing oligonucleotide therapeutics (ONTs). As synthetic drugs, the nonclinical safety evaluation follows ICH guidelines for small molecules which requires the full battery of genotoxicity tests. However, ICHS2(R1) guidance does not specifically refer to ONTs, and these compounds are not expected to interact chemically (e.g., by covalent binding) with DNA or other cellular targets, such as mitotic microtubules, that could result in genotoxicity.

The current literature was reviewed for evidence of various hypothetical mechanisms considered potential hazards for ONT genotoxicity, including effects on deoxyribonucleotide triphosphate pools, integration into DNA, triplex formation, effects on DNA repair and cell cycle regulation. The EFPIA-OWG also identified additional factors for consideration, i.e., 1) ONT class/modality; 2) conjugated targeting ligand/delivery platforms; 3) ONT sequence; and 4) ONT specific chemical modifications. To address these and other factors, an industry survey was undertaken (covering biotech and pharma across US, Europe, and Japan) regarding ONT testing under ICHS2(R1). Preliminary analysis indicates genotoxic effects are not observed with a variety of different ONT chemistries and modalities, confirming previous observations (PMID 26978711, 30139307, 28295562) and expanding on the knowledgebase of well precedented modifications. Initial survey analysis will be presented and placed into context with ONT-specific considerations and testing precedence. The EFPIA-OWG will continue to investigate the survey results and recent literature to build a weight of evidence approach for recommendations regarding future genotoxicity testing requirements.

Keywords:
Oligonucleotide therapeutics, genetic toxicology, EFPIA, PDEG .