## Chromatographic characterisation and impurity analysis of oligonucleotide-based therapeutics and nucleic acid polymers

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Oligonucleotides or longer nucleic acid polymers (NAPs) have emerged as promising drug candidates for various diseases such as cancer, viral infections, and cardiovascular disorders. Antisense oligonucleotides, aptamers, small-interfering RNAs (siRNAs) and polyribonucleotides are currently under evaluation in clinical trials. To ensure efficacy and eliminate possible side effects, regulatory agencies require thorough and effective characterization and quality control of synthetic oligonucleotides and nucleic acid polymers. Often these molecules are chemically modified to improve hydrolytic stability, reduce enzymatic degradation or alter hydrophobicity property for a specific therapeutic activity. The most common modifications to RNA molecules are replacement of phosphodiester (PO) with phosphorothioate (PS) linkages and addition of 2'-O-methyl to ribose. The PS linkage introduces a chiral center at phosphorus. In combination with the chiral centers in D-ribose this produces diastereoisomer pairs at each PS linkage making characterization of these molecules more challenging.
Anion-exchange chromatography and ion-pair reversed-phase chromatography provide strategies that allow the characterization and impurity analysis of synthetically modified oligonucleotides. The presentation will elucidate examples for the analysis of partially and fully phosphorothioated and 2'-O-methylated RNA molecules.