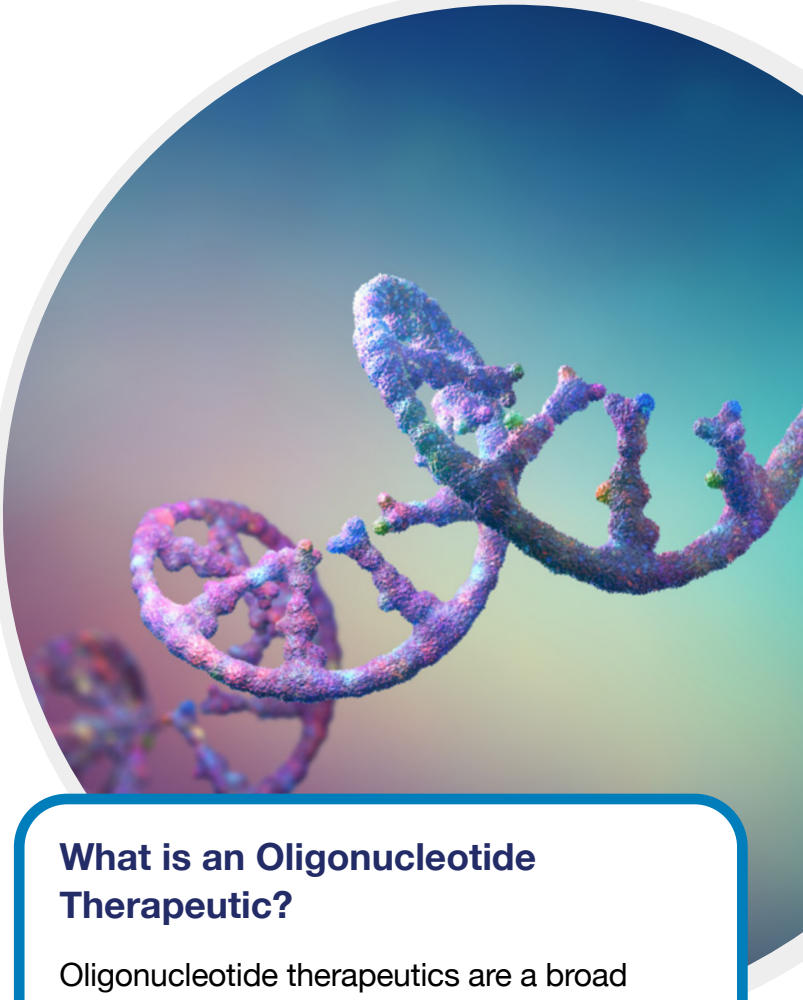
U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics

Final Guidance for Industry



What is Recommended in This Guidance?

This FDA guidance recommends conducting specific clinical pharmacology evaluations during the development of oligonucleotide therapeutics.

Topics covered in the guidance include (1) characterizing the potential for QTc interval prolongation, (2) performing immunogenicity risk assessment, (3) characterizing the impact of hepatic and renal impairment, and (4) assessing the potential for drug-drug interactions.

Why Is This Guidance Important?

This FDA guidance is important because oligonucleotide therapeutics represent a rapidly expanding therapeutic modality with a growing number of drugs in development for treating both rare and common diseases. The recommendations provided herein help to ensure that consistent approaches are utilized in the development of these novel therapies by taking into consideration the unique pharmacological properties and development challenges associated with oligonucleotide therapeutics.

What is an Oligonucleotide Therapeutic?

Oligonucleotide therapeutics are a broad category of synthetically modified RNA or RNA/DNA hybrids designed to specifically bind to target RNA sequences to alter RNA and/or downstream protein expression. These therapeutics can differ in their mechanism of action, structure, chemical modifications, size, sequence, delivery strategy, and the presence or absence of other moieties like small molecules, proteins, or antibodies.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about clinical pharmacology considerations for the development of oligonucleotide therapeutics, **read the guidance**. To see additional Guidance Snapshots, **check out the pilot program**.

Clinical Pharmacology Considerations

Characterizing QTc Interval Prolongation and Proarrhythmic Potential: To date, no large mean effect of oligonucleotide therapeutics on the QTc interval has been observed in the small number dedicated QT studies. However, the variety of these drugs means that available clinical experiences are not sufficient to support an overall conclusion on the proarrhythmic potential of specific types. Therefore, the premarket investigation of a new oligonucleotide therapeutic agent should include an adequate assessment of the drug's effect on the QT/QTc interval. The guidance further specifies that an assessment of QT prolongation risk should be conducted as outlined in other FDA guidances, with all proposals adequately justified and discussed with the Agency.

Characterizing the Impact of Hepatic and Renal Impairment on Pharmacokinetics, Pharmacodynamics, and Safety: To address impact of organ function, the sponsor should identify the role of the liver and kidneys in the disposition, elimination, and drug response based on preliminary data available. This information should guide the enrollment of subjects in late-phase trials. For drugs that are not predominantly renally cleared or that do not target the liver, enrolling patients with a wide range of hepatic or renal function is recommended. When a drug is substantially renally cleared, a reduced pharmacokinetic study design is suggested for severe renal impairment. If the oligonucleotide therapeutic targets the liver, characterizing the impact of hepatic impairment is advised.

Performing Immunogenicity Risk Assessments: The development of oligonucleotide therapeutics is rapidly evolving; new modifications (e.g., chemistry, delivery) can affect immunogenicity risk and assessment approaches. Clinical and nonclinical assessments should follow a risk-based approach and be included in a product-specific immunogenicity risk assessment. Important considerations include product factors, pharmacology of the product, and patient characteristics. Sponsors should discuss their immunogenicity risk assessment and how it informs their clinical immunogenicity assessment for a particular product with the Agency.

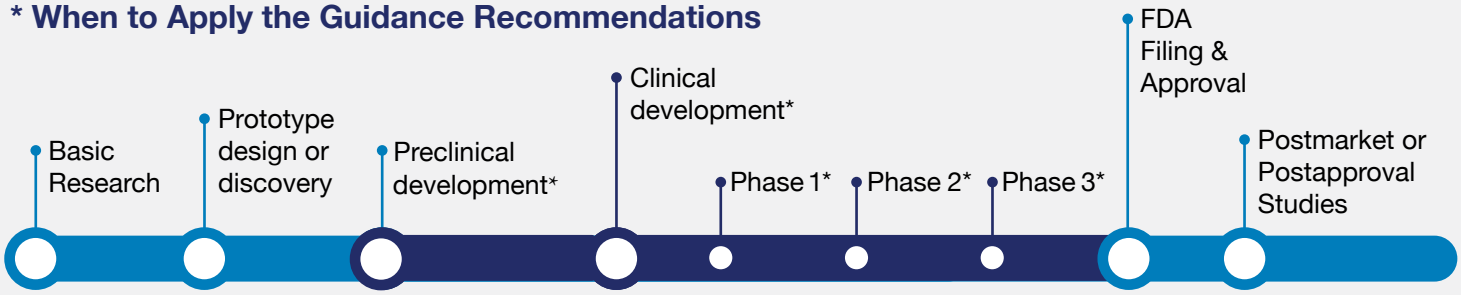
Considerations for Assessing Drug-Drug Interactions: Oligonucleotide therapeutics are not typically metabolized by cytochrome P450 (CYP) enzymes, suggesting minimal interaction potential with CYP modulators. Typically, modulation of transporters is generally not anticipated to have a significant impact. However, the potential for oligonucleotide therapeutics to be an inhibitor and inducer should be evaluated via in vitro assessments. If there is an indication of CYP or transporter modulation in vitro, the sponsor should consider clinical studies to evaluate the drug interaction potential.

Guidance Insights

This guidance is largely based on the recommendations that the Agency is already providing to individual sponsors. As the field of oligonucleotide therapeutics progresses, with innovations such as chemical modifications to bases and/or backbones, structural changes, and new delivery strategies, sponsors are encouraged to reach out to the relevant review divisions with any inquiries concerning the topics addressed in this guidance. The FDA further encourages sponsors to engage in dialogue with the appropriate review divisions during the pre-investigational new drug (pre-IND) application or investigational new drug (IND) application phase to discuss the development of these therapeutics.

Drug Development Timeline

*** When to Apply the Guidance Recommendations**



Recommendations from this guidance typically apply during preclinical through clinical development.

Guidance Recap Podcast

Hear highlights straight from FDA staff

Speakers: Anuradha Ramamoorthy, PhD, Master Scientist, and Hobart Rogers, PhD, Research Officer, in in the Center for Drug Evaluation and Research (CDER), Office of Clinical Pharmacology

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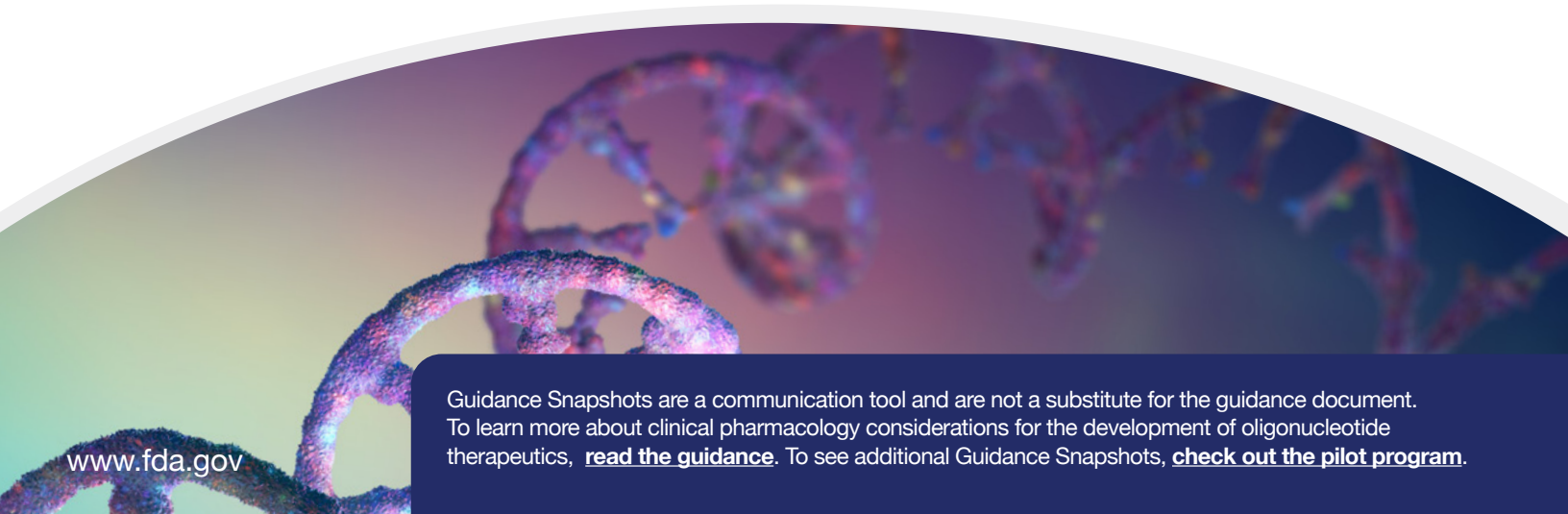

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