For the first time, the FDA has issued a draft guidance for industry on “Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics”. Oligonucleotides are short single or double-stranded fragments of DNA or RNA. In contrast to DNA, oligonucleotides usually contain from 13 to 25 nucleotides, but they can be larger as well. Therapies based on oligonucleotides are relatively new, with a few antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) products being recently approved by FDA and several more in development.

Oligonucleotides include a wide variety of synthetically modified RNA or RNA/DNA hybrids which usually act by altering the target RNA and/or protein expression. Due to the nature of their structure, oligonucleotides cover a wide range due to differences based on mechanism of action, chemical modifications, size, sequence, etc.

This first guidance focuses on oligonucleotides that rely on an RNA-centric mechanism of action based on knowledge gained by the FDA with recent submissions and approvals and is subject to expansion and revisions as the knowledge expands. For most products in this category, a single simplified approach is not feasible or appropriate and consultation with the appropriate review Division at the FDA is encouraged beginning early in the development process.

Since oligonucleotides are complex molecules and have complex profiles, the FDA acknowledges the difficulty in generalizing clinical pharmacology considerations across the class. The FDA suggests that sponsors take into account the overall characteristics of the specific oligonucleotide under development, such as its chemistry, its target site of action, mechanism of action, in vitro data and nonclinical data when developing the overall program and present this to the relevant review division to obtain concurrence. Specific development direction is determined on a case-by-case basis.

The guidance recommends that in general, sponsors characterize the pharmacokinetics early in the development process keeping in mind that the pharmacokinetics may not correlate with the target tissue distribution, pharmacodynamics, safety or efficacy. For this reason, multiple dose studies should also include an assessment of relevant biomarkers.
The guidance provides general considerations in four specific areas: QTc prolongation, immunogenicity, hepatic and renal impairment and drug-drug interaction (DDI).

Although the data to date indicates that oligonucleotides do not typically have an effect on cardiac activity including QTc prolongation and proarrhythmic effects, it is important to develop an assessment plan in line with the FDA guidance entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” dated October 2012 and discuss this plan with FDA.

An immune response may be generated for a variety of reasons including the oligonucleotide itself or its carrier. A risk-based approach for clinical immunogenicity assessment is recommended in line with the FDA guidance entitled “Immunogenicity Assessment for Therapeutic Protein Products” dated August 2014. Sponsors should discuss their immunogenicity risk assessment plan with the FDA to determine the appropriate approach.

The role of the liver and the kidney in the disposition and elimination of the oligonucleotide should be evaluated early in the development program based on in vitro and nonclinical data. This will help determine the appropriate approach to assess the impact of hepatic and renal impairment on the clearance of the oligonucleotide in humans. Due to the potential for changes in pharmacodynamics independent of the changes in the pharmacokinetics, it is important to include pharmacodynamic assessments.

For oligonucleotide therapeutics, there are several possible mechanisms for DDI. Although direct effects of cytochrome P450 enzymes or various transporters on the pharmacokinetics of an oligonucleotide is minimal and generally not anticipated, these should be assessed as described in the guidance entitled “In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions” dated January 2020. The potential of an oligonucleotide therapeutic to modulate CYP enzymes or transporters directly or indirectly should be evaluated. In addition to the usual pharmacokinetic DDI, there is also a potential for pharmacodynamic DDI and this should also be discussed with the FDA.

Oligonucleotide therapeutics represent a relatively new but significant class of therapeutic agents especially those directed towards rare diseases and genetic disorders. The experts at ProPharma Group can help you navigate the complex and unique development issues of oligonucleotide therapeutics and develop a comprehensive strategy for success.

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