



# Non-clinical Experience with RNA-based Oligonucleotide Therapeutics

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# Disclaimer

*The views expressed in this presentation are that of the presenter and do not represent the opinions of the U.S. Government or the Food and Drug Administration (FDA)*

# Outline

- The regulation of non-clinical studies for Investigational New Drugs (IND) and New Drug Applications (NDA)
- Experience with RNA-based therapeutics in CDER
- Mechanisms to monitor progress and issues relating to oligonucleotide therapeutics

# Regulation of non-clinical drug development in CDER

- CDER guides the entry of small molecules and large molecules into clinical trials.
  - Excludes products that are promoter driven (CBER)
- Non-clinical study requirements are graduated with the level of clinical development.
  - IND-enabling vs. Phase 3 studies vs. NDA submission
- Specific considerations guide development
  - Patient population
  - Risk/benefit
  - Duration of use

# Guidances for Drug Regulation

- ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
- ICH S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- ICH S5 A and B – Detection of Reproductive Toxicity to Reproduction for Medicinal Products
- ICH S7A and B – Safety Pharmacology Studies for Human Pharmaceuticals

# Non-clinical assessments

## Pharmacology

- Exaggerated, Secondary, Pharmacodynamic interactions

## Safety Pharmacology

- CV, Respiratory, CNS, Renal, GI systems

## Toxicology

- Single dose, Repeat dose, and Chronic dose (3, 6 or 9 months) toxicology studies in two species

## Genetic Toxicology

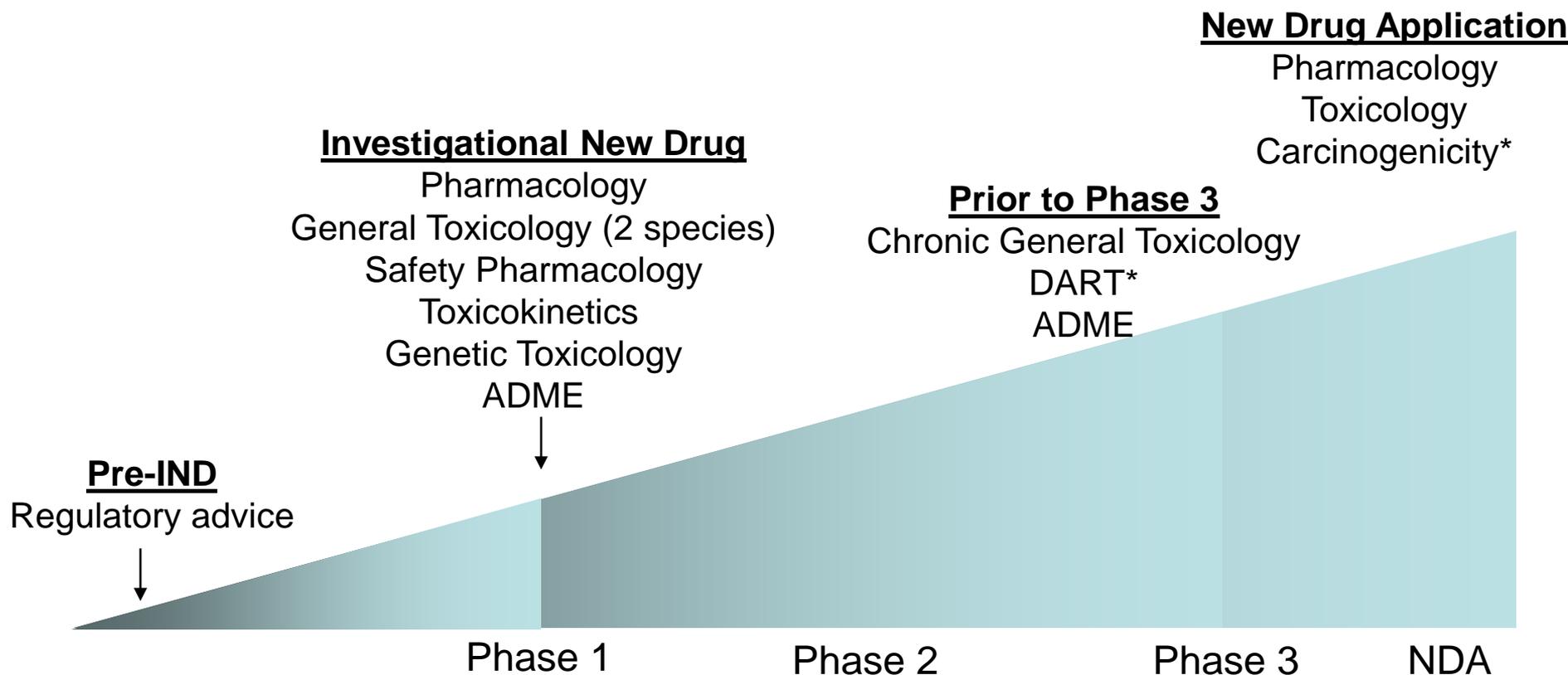
- *in vitro* and *in vivo* assays (per new ICH S2 (R1))

## Reproductive Toxicology

- Fertility/mating, developmental toxicity, and pre-postnatal toxicity

## Carcinogenicity

# Studies as development proceeds



\*Requirements on case-by-case

# Study Design Elements

The studies for small molecules and oligonucleotides are similar in nature but may differ in design elements

## Negative controls

- PBS, scrambled sequence, vehicle, etc.
- Formulation-related effects

## Species relevance

- Species may not share sequence homology with the clinical candidate.
- Can be addressed by surrogate sequences

## Sequence-independent toxicities (backbone chemistry, formulation)

- Liver, kidney, immune toxicities can be characterized in general toxicology studies

## Off-target effects

- *In silico and/or in vitro* assessments



# *Current experience with oligonucleotides*

# Current Non-clinical Experience with siRNA products

- 20 years experience with DNA-based oligonucleotides serves as a background for our current experience.
- Number of siRNA applications (+/-15)
  - Drug products differ in their backbone chemistries, formulations, route of administration, patient populations
- Following a regulatory framework that is fairly typical of small molecule drugs.



# Current Experience with siRNA

A database is being kept to monitor the nature of oligonucleotides, how they are being tested, and results of those tests.

Parameters include:

## General

IND Number  
Division  
Oligo Name  
Sequence (5'-3')  
Chemical Modification  
Pharmacologic Target  
Description (Oligo Class)  
Impurity Issue?

## Toxicology

Species (# mismatches?)  
Disease Model?  
Dose/schedule  
Duration  
Surrogate Sequence (Y/N)  
Administration Route  
Negative control/Formulation  
Notable Tox

## Start Dose

Which species?  
mg/kg or mg/m<sup>2</sup>?  
Based on NOAEL?

## Trials

DLT (also in nonclin?)  
Dose escalation  
Schedule  
MTD  
Clinical hold?

## Other

Immunogenicity  
Miscellaneous notes

# Experience across indications

## Indications

Ocular  
Oncology  
Renal  
Anti-viral  
Skin  
Vascular  
Pulmonary

## Routes

Intravitreal  
Intravenous  
Subcutaneous  
Inhalation

## Targets

Kinases (S/T, RTK)  
Soluble proteins  
Transcription Factors  
Viral  
Other

# Common Toxicities

- Toxicities vary based on sequence, formulation, frequency, duration and route of administration.
- Common toxicities include:
  - Liver
    - i.e. Histopath findings of single cell necrosis, inflammatory cell infiltration, liver weight increase, ALT and AST elevations
  - Kidney
    - i.e. Histopath findings of degeneration and inflammatory cell infiltrates, increased BUN and changes in electrolytes
  - Inflammation
    - Evident in histopath findings, hematology parameters, separate *in vitro* assays
    - At times: complement activation, cytokine release

# Broad Overview of Results

## Safety Pharmacology

- No trend of toxicity in safety pharmacology tests across applications (i.e. CNS, CV, pulmonary).

## Genetox studies

- Drug products thus far have tested negative for mutagenicity or clastogenicity

## Pharmacokinetics

- C<sub>max</sub> related toxicities (complement, APTT), and toxicities in organs of major distribution.
- Formulations may alter distribution and PK parameters may vary among species.

## Impurities

- Elevated impurities in the drug product undergo a safety evaluation per ICH Q3A and B.

# Off-Target Effects Assessments

- Hybridization of oligo nucleotides to sequences other than their intended target.
- Recognized as a potential source of toxicity
- Current methods for assessing OTE are typically *in silico* at times followed by *in vitro* tests
- Complexities include – search engine, degree of homology, and sequences “of interest”
  - These factors currently preclude a prescriptive method for evaluation of OTEs

# Reproductive and Developmental Toxicity

- The experience is limited; these studies are submitted in the later stages of drug development
- Current approach is per ICH M3(R2)
  - Fertility and embryo-fetal developmental toxicity studies are completed prior to Phase 3. (ICH S5A and B)
  - Women of child-bearing potential should be tested for pregnancy status prior to enrollment and during trial and utilize a highly effective method of contraception.
  - Pre-postnatal developmental effects are assessed prior to marketing approval. (ICH S5A and B)
    - Prenatal and postnatal death of offspring
    - Altered growth and development
    - Measuring functional deficits in offspring (behavior, maturation (puberty) and reproduction (F1)).
- Use of surrogate sequence may be appropriate.



# ***Oligo-related Initiatives***

# FDA PTCC Oligonucleotide Subcommittee

- Monthly meetings present an open internal forum for discussion of oligo-related issues.
- Membership includes a P/T reviewer from each division of OND in CDER
  - Resource for primary reviewers
- Monitoring past experience and current trends
- Discussion of emerging issues
  - Upcoming meetings, interesting applications, publications and white papers
  - Invited speakers, course under development

# FDA/DIA Oligonucleotide Symposium 2012

- A symposium held once every two years which is sponsored by FDA, Health Canada, AAPS, OTS, and DIA.
- Participants include members from FDA, Health Canada, BfArM, NIH-RAC, and industry.
- Goals: discuss safety, developmental challenges, and emerging technologies for oligonucleotides.
  - Three tracks: Nonclinical, CMC and Clinical
- Takes place April 16<sup>th</sup> to 18<sup>th</sup>, 2012.

# Summary

- The FDA has a regulatory framework which guides the introduction of oligonucleotide therapeutics into clinical trials.
  - A graduated system requires more intensive studies before introduction into larger populations.
- Our database has not currently identified safety signals in nonclinical testing
- The regulatory framework, internal FDA PTCC Oligo Subcommittee, and participation in coordination of the FDA/DIA Oligo meeting are mechanisms to monitor emergent issues.