DIA/FDA Oligonucleotide-Based Therapeutics Conference

October 25-27 | Bethesda North Marriott Hotel and Conference Center | North Bethesda, MD

PROGRAM CO-CHAIRS

James Thompson, PhD
Head, CMC Project Management
Moderna Therapeutics

James Wild, PhD
Pharmacologist
CDER, FDA

PROGRAM COMMITTEE

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CDER, FDA

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Chief, Branch I, DPMA1, OLDP, OPQ
CDER, FDA

Kim Tyndall
Director of CMC Regulatory Affairs
GlaxoSmithKline

Overview

The *DIA/FDA Oligonucleotide-Based Therapeutics Conference* fosters open discussion with industry and health authorities to inform, educate, and share advancements in oligonucleotide-based therapeutic product development. Designed for regulators and industry from CMC, Nonclinical, Clinical Pharmacology, and Clinical disciplines, the conference will address developmental advances, safety, and challenges in the field of oligonucleotide-based therapeutics.

Highlights

- Keynote Addresses from **Arthur M. Krieg**, MD, President and CEO, Checkmate Pharmaceuticals, and **Philip J. Brooks**, PhD, Program Director, Division of Clinical Innovation National Center for Advancing Translational Sciences (NCATS)
- National Institutes of Health representation
- Poster Session
- Special luncheon presentation featuring the Japanese Perspective on Preclinical Safety Assessment of Oligonucleotide Therapeutics
- **NEW:** Luncheon Round Table Discussions on cutting-edge topics with key thought leaders
- **NEW:** Oligo Safety Working Group (OSWG) open meeting
- **NEW:** Visit exhibiting companies during the networking breaks
- Breakfast Session on Thursday, 8:15-9:00AM, on Emergency Single Patient IND for Oligonucleotide Therapy of a Unique Individual Mutation

Who Should Attend

Senior-level professionals and those working in the following areas of oligonucleotide science:

- Drug Discovery
- Preclinical
- Clinical
- CMC
- Quality Assurance
- RNAi
- Vaccines
- Biotechnology
- Delivery Technologies
- Clinical Pharmacology/Research

A Message from the Program Committee

Dear Colleagues,

We are pleased to welcome you to the *DIA/FDA Oligonucleotide-Based Therapeutics Conference*!

This conference is unique in setting the stage for an open, collaborative discussion of important topics and tools for senior-level professionals and those working in oligonucleotide science to navigate the dynamic and quickly changing health care environment. Experts across three central tracks, CMC, Nonclinical, and Clinical, will be presenting in-depth information. We are truly three meetings in one, with plenaries planned to create a cross-functional experience for knowledge-sharing, integrated thought leadership, and proactive networking.

The conference will begin with a cross-track plenary session featuring the emerging landscape of mRNA-based drugs which is immediately followed by track-specific breakout sessions and ending with a poster session and welcome reception.

Day two will open with two Keynote Addresses from Arthur M. Krieg, MD, President and CEO, Checkmate Pharmaceuticals, and Philip J. Brooks, PhD, Program Director, Division of Clinical Innovation National Center for Advancing Translational Sciences (NCATS), who will be discussing the current state of oligonucleotides within FDA and NIH.

We hope you will take advantage of the many opportunities to actively engage in discussions and with each other. Be sure to join us Wednesday evening for the Poster Session and Networking Reception, Thursday during the luncheon to participate in a round table discussion, or join a session inspired by colleagues in Japan to learn more about their perspective on preclinical safety assessment of oligonucleotide therapeutics in comparison with biopharmaceuticals and low molecular new chemical entities. Thursday evening we have an open meeting of the DIA Oligonucleotide Safety Working Group (OSWG). Finally, at the closing session on Friday, leaders from each of the three tracks will come together to highlight key takeaways and moderate an open Q&A with the audience.

Best Regards,
The DIA/FDA Oligonucleotide Program Committee

Schedule At-A-Glance

Track A: CMC **Track B:** Nonclinical **Track C:** Clinical

DAY ONE | WEDNESDAY, OCTOBER 25		ROOM
7:00AM-5:00PM	Registration	Grand Ballroom Salon C Foyer
7:00-8:00AM	Continental Breakfast, Exhibits, and Networking	Grand Ballroom Salon D
8:00-8:30AM	**Welcome Remarks and Overview of the 2017 Conference**	Grand Ballroom Salon A-C
8:30-10:30AM	**Session 1:** The Emerging Landscape of mRNA-Based Drugs: A New Modality in Vaccines and Therapeutics	Grand Ballroom Salon A-C
10:30-11:00AM	Refreshment, Exhibits, and Networking Break	Grand Ballroom Salon D
11:00AM-12:30PM	**Session 2:** Concurrent Breakout Sessions	
	Track A: Control Strategy for Double-Stranded Oligonucleotides	Grand Ballroom Salon C
	Track B: Assessing the Implications of Oligonucleotide Uptake into Cells	Grand Ballroom Salon A/B
	Track C: Cardiovascular/Metabolic Diseases	Brookside, Lower Level
12:30-1:30PM	Luncheon, Exhibits, and Networking	Grand Ballroom Salon D
1:30-3:00PM	**Session 3:** Concurrent Breakout Sessions	
	Track A: Starting Materials: Beyond Simple DNA and RNA Derived Phosphoramidites	Grand Ballroom Salon C
	Track B: Understanding the Effects of 2'-MOE ASO Treatment on PLT Count in Non-Human Primates and Humans	Grand Ballroom Salon A/B
	Track C: New Approaches in the Development of Immune Stimulatory Oligonucleotides in Oncology	Brookside, Lower Level
3:00-3:30PM	Refreshment, Exhibits, and Networking Break	Grand Ballroom Salon D
3:30-5:00PM	**Session 4:** Concurrent Breakout Sessions	
	Tracks A/B: Chemistry and Safety Considerations for Impurities in Oligonucleotide Therapeutics	Grand Ballroom Salon A-C
	Track C: Clinical Advances in Oligonucleotide-Based Therapies for Neuromuscular Diseases	Brookside, Lower Level
5:00-6:00PM	Poster Session and Networking Reception	

DAY TWO | THURSDAY, OCTOBER 26		ROOM
8:00AM-5:00PM	Registration	Grand Ballroom Salon C Foyer
8:00-9:00AM	Continental Breakfast, Exhibits, and Networking	Grand Ballroom Salon D
8:15-9:00AM	**Breakfast Plenary Session:** Emergency Single Patient IND for Oligonucleotide Therapy of a Unique Individual Mutation	Grand Ballroom Salon A-C
9:00-9:05AM	**Welcome to Day Two**	Grand Ballroom Salon A-C
9:05-10:05AM	**Session 5:** Keynote Addresses	Grand Ballroom Salon A-C
10:05-10:30AM	Refreshments, Exhibits and Networking Break	Grand Ballroom Salon D
10:30AM-12:00PM	**Session 6:** Concurrent Breakout Sessions	
	Track A: Thinking Ahead: Oligonucleotide Drug-Device Combination Products	Grand Ballroom Salon C
	Tracks B/C: What, Where, and How: Biomarkers Inform Disease Targets, Biodistribution, and Function of Oligonucleotide Therapeutics	Grand Ballroom Salon A/B
12:00-1:30PM	Round Table Discussion Luncheon, Exhibits, and Networking	Grand Ballroom Salon D
12:00-1:15PM	**Luncheon Presentation:** Japanese Perspective on the Preclinical Safety Assessment of Oligonucleotide Therapeutics	Grand Ballroom Salon D
1:30-3:00PM	**Session 7:** Concurrent Breakout Sessions	
	Track A: Recently Approved and Late-Stage Oligonucleotide Drugs	Grand Ballroom Salon C
	Tracks B/C: Predicting Cinical Safety from Nonclinical Data: Case Studies	Grand Ballroom Salon A/B
3:00-3:30PM	Refreshment, Exhibits, and Networking Break	Grand Ballroom Salon D
3:30-5:00PM	**Session 8:** Gene Editing	Grand Ballroom Salon A-C
5:00-5:30PM	**DIA Oligonucleotide Safety Working Group (OSWG) – Open Meeting**	Brookside, Lower Level

DAY THREE | FRIDAY, OCTOBER 27		ROOM
7:00AM-12:00PM	Registration	Grand Ballroom Salon C Foyer
7:00-8:00AM	Continental Breakfast and Networking	Grand Ballroom Salon D
8:00-9:30AM	**Session 9:** Concurrent Breakout Sessions	
	Track A: Interactive Discussion of CMC Challenges and Moving Forward	Grand Ballroom Salon C
	Tracks B/C: Expanding Therapeutic Utility via Targeted Delivery	Grand Ballroom Salon A/B
9:30-9:45AM	Refreshment and Networking Break	Grand Ballroom Salon D Foyer
9:45-11:15AM	**Session 10:** Hot Topics in Oligonucleotide Therapeutics	Grand Ballroom Salon A-C
11:15AM-12:00PM	**Closing Session:** Panel Discussion	Grand Ballroom Salon A-C

Learning objectives

At the conclusion of this conference, participants should be able to:

- Identify accomplishments and challenges in the clinical development of oligonucleotide-based therapeutic drugs
- Describe the critical issues in the nonclinical development of oligonucleotides
- Differentiate the chemistry, manufacturing, and controls challenges associated with the development of synthetic oligonucleotides, including formulation and specification issues
- Explain unique aspects and various scientific approaches used during the development of oligonucleotide-based therapeutics
- Recognize the achievements made in the field to date and be able to share the vision with patients about the therapeutic potential that oligonucleotides possess across a wide range of indications

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DAY ONE | WEDNESDAY, OCTOBER 25

7:00AM-5:00PM — **Registration**

7:00-8:00AM — **Continental Breakfast, Exhibits, and Networking**

8:00-8:30AM — **Welcome Remarks and Overview of the 2017 Conference**

Sudip Parikh, PhD
Senior Vice President
DIA

James Thompson, PhD
Head, CMC Project Management
Moderna Therapeutics

James Wild, PhD
Pharmacologist
CDER, FDA

8:30-10:30AM — **Session 1**

The Emerging Landscape of mRNA-Based Drugs: A New Modality in Vaccines and Therapeutics

Session Co-Chairs

Tal Zaks, MD, PhD
Chief Medical Officer
Moderna Therapeutics

Ramachandra G Naik, MD
Primary Reviewer/Regulatory Project Manager, OVRR
CBER, FDA

mRNA therapeutics are unique, relative to most oligonucleotide-based modalities like antisense, siRNAs, and aptapers in that mRNAs enable expression of the encoded protein rather than act as antagonists to inhibit target protein translation or activity. Early clinical data indicate that mRNA-based drugs may be effective vaccines and their potential as therapeutics is now emerging. This session will describe the general approach to mRNA manufacture, present emerging preclinical and clinical data on mRNA vaccines and therapeutics, and provide a regulatory perspective on the product-related (CMC) aspects of mRNA drug development.

Translating mRNA Vaccines and Therapeutics: First Clinical Steps

Tal Zaks, MD, PhD
Chief Medical Officer
Moderna Therapeutics

Clinical Development of mRNA Vaccines and Immunotherapies: Experiences and Lessons Learned

Ulrike Gnad-Vogt, MD
Chief Medical Officer
CureVac AG, Germany

Regulatory Perspective on the Product-Related (CMC) Aspects of mRNA Vaccines

Keith Peden, PhD
Chief, Laboratory of DNA Viruses
CBER, FDA

Considerations for the Nonclinical Development of Systemically-Administered Therapeutic mRNA

Sarah Beach Voytek, PhD
Principal Scientist
Novartis Institutes For Biomedical Research, Inc.

Panel Discussion

10:30-11:00AM — **Refreshment, Exhibits, and Networking Break**

11:00AM-12:30PM

Session 2
Concurrent Breakout Sessions

TRACK A
Control Strategy for Double-Stranded Oligonucleotides

Session Chair

Samantha Gao-Sheridan, PhD
Senior Director, Regulatory Affairs CMC
Alnylam Pharmaceuticals

Focus on the control strategy elements to be considered for the development and registration of double-stranded oligonucleotide therapies. Joined by both industry and regulatory agency presenters and panelists, this session will review and discuss the key principles and challenges in the double-stranded oligonucleotide API and drug product process control strategy (e.g., control of impurities, annealing, sterilization), as well as analytical development and product life cycle management. Both oligonucleotide conjugates and other different drug product formulations will be considered.

European Regulatory Perspective on Double-Stranded Oligonucleotides

René Thürmer, PhD
Deputy Head of the Unit Pharmaceutical Biotechnology
BfArM - Federal Institute for Drugs and Medical Devices, Germany

Characterization and Control of siRNA Impurities

Matthias Kretschmer, PhD
Senior Director, Analytical Development
Alnylam Pharmaceuticals

Panel Discussion

Joining the speakers:

Ramesh Raghavachari, PhD
Chief, Branch I, DPMA1, OLDP, OPQ
CDER, FDA

Vidhya Gopalakrishnan, PhD
Senior Vice President, Pharmaceutical Development
Quark Pharmaceuticals

TRACK B
Assessing the Implications of Oligonucleotide Uptake into Cells

Session Co-Chairs

Xuan Chi, MD, PhD
Pharmacology/Toxicology Reviewer, Division of Cardiovascular and Renal Products, Office of New Drugs
CDER, FDA

Jeffery A. Engelhardt, DVM, PhD, DACVP, FIATP
Vice President, Pathology and Nonclinical Drug Safety
Ionis Pharmaceuticals, Inc.

Examine the cellular uptake and lysosomal processing of single-stranded oligonucleotides by the most frequently affected tissues and cells following systemic administration (kidney and macrophages) and intrathecal administration (neurons). The histopathologic changes associated with uptake will be presented and discussed relative to assessing adversity of the findings. The conclusion of the European Society of Toxicologic Pathology (ESTP) expert panel on adversity of lysosomal accumulation relative to oligonucleotides will also be discussed.

Renal and Macrophage Uptake of Systemically Administered Oligonucleotides

Kendall Frazier, DVM, PhD
Director, Cellular and Molecular Pathology
GlaxoSmithKline

Neuronal Uptake of Intrathecally Administered Oligonucleotides

Jeffery A. Engelhardt, DVM, PhD, DACVP, FIATP
Vice President, Pathology and Nonclinical Drug Safety
Ionis Pharmaceuticals, Inc.

A Report from the ESTP Expert Panel on Adversity of Lysosomal Accumulation

James Willard, PhD
Pharmacologist, DCaRP
CDER, FDA

Panel Discussion

Joining the speakers:

Vidhya Gopalakrishnan, PhD
Senior Vice President, Pharmaceutical Development
Quark Pharmaceuticals, Inc.

TRACK C
Cardiovascular/Metabolic Diseases

Session Co-Chairs

Peter Wijngaard, PhD
Senior Vice President, ACC GIG Health Science Leader
The Medicines Company

Elena Braithwaite, PhD, DABT
Toxicologist
FDA

Review progress made in the clinical development of RNA therapeutics in the cardiovascular and metabolic therapeutic areas. The targets and applications range from Factor XI antagonism in the coagulation pathway using antisense oligonucleotides to the inhibition of PCSK9 synthesis via RNA interference and GalNAc conjugation to reduce cardiovascular risk factors.

Antisense Reduction of FXI for Thromboprophylaxis: A Novel Therapeutic Approach

Sanjay Bhanot, MD, PhD
Vice President, Metabolic Diseases, Research and Development
Ionis Pharmaceuticals, Inc.

Volanesorsen: Targeting ApoC-III for Treatment of Patients with Familial Chylomicronemia Syndrome (FCS)

Louis St.L. O'Dea, MB, BCh, BAO, CSPQ, FRCPC
Executive Vice President, Chief Medical Officer and Head, Regulatory Affairs
AKCEA Therapeutics

PCSK9 Synthesis Inhibition: siRNA Therapeutic for Large Indications

Peter Wijngaard, PhD
Senior Vice President, ACC GIG Health Science Leader
The Medicines Company

Panel Discussion

12:30-1:30PM

Luncheon, Exhibits, and Networking

1:30-3:00PM

Session 3
Concurrent Breakout Sessions

TRACK A
Starting Materials: Beyond Simple DNA and RNA Derived Phosphoramidites

Session Chair
Fran Wincott, PhD
President
Wincott & Associates, LLC

There has been a dramatic increase in the complexity of drug candidates being promoted into preclinical and clinical development. These oligonucleotides often have significant chemical modifications requiring specialty starting materials. Furthermore, recent communications from regulatory authorities regarding the selection and justification of starting materials have been issued. This session will address the general starting material principles outlined in Q11 and the accompanying Q&A document. In addition, strategies for defining and sourcing non-standard oligonucleotide-specific starting materials will be presented. The presentations will be followed by a 30 minute panel discussion.

Identification of Starting Materials for Oligonucleotides by Applying ICH Q11

Timothy J. N. Watson, PhD
Senior Director, CMC Advisory Office
Pfizer Inc

Integrating LNA Phosphoramidites into the Regular Supply Chain

Christoph Rosenbohm, PhD, MBA
Vice President, Head of Discovery Operations
Roche Innovation Center
Copenhagen, Denmark

GalNAc Solid Support as Starting Material for Oligonucleotide Manufacturing

Lubomir Nechev, PhD
Vice President, Process Sciences
Alnylam Pharmaceuticals

Panel Discussion

Joining the speakers:

Olen Stephens, PhD
Chemist
CDER, FDA

René Thürmer, PhD
Deputy Head of the Unit, Pharmaceutical Biotechnology
BfArM - Federal Institute for Drugs and Medical Devices, Germany

TRACK B
Understanding the Effects of 2'-MOE ASO Treatment on PLT Count in Non-Human Primates and Humans

Session Co-Chairs
Scott Henry, PhD, DABT
Vice President, Nonclinical Development
Ionis Pharmaceuticals, Inc.

Ronald L. Wange, PhD
Pharmacology and Toxicology, Reviewer, Division of Metabolism and Endocrinology Products
FDA

Examine the overall experience with this class of oligonucleotides on PLT count in both monkeys and humans using a database comprised of multiple compounds. Comparisons will be made between monkeys and humans, include special patient populations that have recently reported severe thrombocytopenia. Background information on PLT biology and the current status investigation into the mechanism of potential PLT changes will be presented.

PLT Biology 101: Platelets and the Immune Continuum

Joseph E. Italiano, PhD
Director Cellular and Molecular Pathology
Division of Hematology
Brigham and Women's Hospital

Characterizing the Nature and the Mechanism of PLT Changes Observed in Monkeys Treated with 2' MOE ASO

Scott Henry, PhD, DABT
Vice President Nonclinical Drug Development
Ionis Pharmaceuticals Inc.

Human PLT Database for 2'-MOE ASO and Recent Experience in FCS and TTR Phase 3 Trials

Richard Geary, PhD
Executive Vice President, Drug Development
Ionis Pharmaceuticals Inc.

Panel Discussion

TRACK C
New Approaches in the Development of Immune Stimulatory Oligonucleotides in Oncology

Session Co-Chairs
Arthur M. Krieg, MD
President and CEO
Checkmate Pharmaceuticals

Emily J. Place, PhD, MPH
Pharmacologist, Office of New Drugs
CDER, FDA

The innate immune system has evolved multiple different receptors for the detection of viral or bacterial RNA and DNA including several Toll-like receptors (TLR), the RIG-I family of helicases, cGAS, and others. These receptors trigger both T cell and B cell adaptive immune responses that are capable of killing infected host cells. Synthetic nucleic acids that activate several different innate immune receptors are in clinical development for the purpose of triggering innate immune resposnes against tumor antigens in subjects with cancer.

Making "Cold" Tumors "Hot" with Intratumoral Injections of a CpG-A Oligonucleotide Packaged in a VLP

Arthur M. Krieg, MD
President and CEO
Checkmate Pharmaceuticals

Exploiting the TLR9 Pathway to Overcome Tumor Immune Ignorances

Jonathan Yingling
Senior Vice President Early Development
Idera Pharmaceuticals

Cancer Immunotherapy: Individualized mRNA-Based Vaccines for the Treatment of Cancer

Matthias Miller, PhD
Project Manager
BioNTech RNA Pharmaceuticals GmbH, Germany

Panel Discussion

3:00-3:30PM — **Refreshment, Exhibits, and Networking Break**

3:30-5:00PM

Session 4
Concurrent Breakout Sessions

TRACK A/B
Chemistry and Safety Considerations for Impurities in Oligonucleotide Therapeutics

Session Chair
Andrew Teasdale, PhD
Chair AZ Impurities Advisory Group
AstraZeneca, United Kingdom

Members of the Oligonucleotide Safety Working Group (OSWG) met regularly over the past 12 months to discuss oligonucleotide impurities. This joint session for the CMC and nonclinical tracks will feature two presentations that attempt to summarize the output of these discussions. Chemistry and safety aspects of oligonucleotide impurities will be presented. The presentations will be followed by a 30 minute panel discussion. Questions for discussion may include:

- What types of oligonucleotide impurities are commonly observed?
- What are appropriate characterization expectations for oligonucleotide impurities?
- What are appropriate reporting, identification, and qualification thresholds for oligonucleotide therapeutics?
- How should oligonucleotide impurities be qualified?
- Can platform data be used to help characterize and qualify oligonucleotide impurities?

Chemistry Considerations for Oligonucleotide Impurities

Daniel Capaldi, PhD
Vice President, Analytical and Process Development
Ionis Pharmaceuticals, Inc.

Safety Considerations for Oligonucleotide Impurities

Scott Henry, PhD, DABT
Vice President, Nonclinical Development
Ionis Pharmaceuticals, Inc.

Panel Discussion

Joining the speakers

James Wild, PhD
Pharmacologist
CDER, FDA

Cathaline Den Besten
Senior Director, Head Toxicology, ADME, PK
Proqr Therapeutics, The Netherlands

TRACK C
Clinical Advances in Oligonucleotide-Based Therapies for Neuromuscular Diseases

Session Co-Chairs
Saraswathy V. Nochur, PhD, MSc
Senior Vice President, Regulatory Affairs and QA
Alnylam Pharmaceuticals, Inc.

Lois M. Freed, PhD
Supervisory Pharmacologist
CDER, FDA

Several oligonucleotide-based therapeutic candidates have been evaluated in the clinic for the treatment of neuromuscular diseases, including two for rare diseases. This session will explore the development of three different molecules, one about to enter the clinic, another getting ready for NDA, and a third that has been approved by FDA and EMA. While each of the disease states for these agents are distinct, there are similarities in the clinical development strategies and the challenges faced. Clinical data will be shared.

Development and Approval of Nusinersen for Spinal Muscular Atrophy: Challenges and Successful Strategies

Wildon R. Farwell, MD, MPH
Senior Director, Clinical Development
Biogen

Hereditary ATTR Amyloidosis: Long-Term Clinical Experience with Patisiran, an Investigational RNAi Therapeutic, in an Open Label Study

John L. Berk, MD
Associate Professor of Medicine, Boston University School of Medicine; Assistant Director, Boston University School of Medicine Amyloidosis Center
Boston University

Development of Ionis-MAPTRx, the First Tau-Lowering Antisense Oligonucleotide, in Patients with Mild AD

Laurence Mignon, PhD
Director, Clinical Development
Ionis Pharmaceuticals, Inc.

Panel Discussion

5:00-6:00PM

Poster Session and Networking Reception

DAY TWO | THURSDAY, OCTOBER 26

8:00AM-5:00PM — **Registration**

8:00-9:00AM — **Continental Breakfast, Exhibits, and Networking**

8:15-9:00AM — **Breakfast Plenary Session**

Emergency Single Patient IND for Oligonucleotide Therapy of a Unique Individual Mutation: A Case Study in Batten's Disease

Session Chair

Arthur M. Krieg, MD
President and CEO
Checkmate Pharmaceuticals

Tim W. Yu, MD, PhD
Division of Genetics and Genomics, Boston Children's Hospital;
Assistant Professor, Harvard Medical School;
Associate Member, Broad Institute

9:00-9:05AM — **Welcome to Day Two**

James Thompson, PhD
Head, CMC Project Management
Moderna Therapeutics

9:05-10:05AM — **Session 5**

Keynote Addresses

Session Co-Chairs

James Wild, PhD
Pharmacologist
CDER, FDA

James Thompson, PhD
Head, CMC Project Management
Moderna Therapeutics

Keynote Speakers

Arthur M. Krieg, MD
President and CEO
Checkmate Pharmaceuticals

Philip J. Brooks, PhD
Program Director, Division of Clinical Innovation
National Center for Advancing Translational Sciences (NCATS), National Institutes of Health

10:05-10:30AM — **Refreshment, Exhibits, and Networking Break**

10:30AM-12:00PM — **Session 6**

Concurrent Breakout Sessions

TRACK A
Thinking Ahead: Oligonucleotide Drug-Device Combination Products

Session Chair

Mohan Sapru, MS, PhD
CMC Lead, Office of Pharmaceutical Quality
CDER, FDA

The session is aimed to broadly discuss oligonucleotide drug-device combination products, an emerging trend in oligonucleotide-based therapeutics, from industry and regulatory perspectives. Specifically, the presentations and panel discussion will focus on:

- Industry perspective concerning salient considerations and challenges of developing drug-device combination products for oligonucleotide therapeutics
- Design control, drug-device verification, and validation processes
- Promises and challenges in using drug/device combination approach for targeted oligonucleotide drug delivery
- Strategies for ensuring product quality, including uniformity of dose delivery, under conditions of use
- Regulatory perspective concerning human factors studies and related clinical study considerations in combination product design and development

Development Considerations for Oligonucleotide Combination Products

Bret Coldren, PhD
Director, Pharmaceutical Development
Ionis Pharmaceuticals

Human Factors Studies - Related Considerations in Combination Product Design and Development

Quynh Nhu Nguyen, MS
Associate Director for Human Factors, Division of Medication Error Prevention and Analysis (DMEPA)
CDER, FDA

Panel Discussion

Joining the speakers:

Ryan McGowan
Associate Director, Combination Products
AstraZeneca

TRACK B/C
What, Where, and How: Biomarkers Inform Disease Targets, Biodistribution, and Function of Oligonucleotide Therapeutics

Session Co-Chairs

Aimee L. Jackson, PhD
Senior Director of Research
miRagen Therapeutics, Inc.

Imran Khan, PhD
Pharmacologist, OMPT, OND, ODEI, DPP
CDER, FDA

This session will present preclinical and clinical data on the identification and validation of biomarkers for oligonucleotide therapeutics. Discussions will include methods to identify pharmacodynamic biomarkers, use of biomarkers to define PK/PD and dose-response relationships, the application of biomarkers to establish mechanistic proof-of-concept and guide dose optimization, and how biomarkers can inform disease status and patient enrichment.

Translating PD Biomarkers from Preclinical Studies to Clinical Trials: MRG-106, an Oligonucleotide Inhibitor of miR-155, Coordinately Regulates Multiple Survival Pathways to Reduce Cellular Proliferation, and Survival in Cutaneous T-Cell Lymphoma

Aimee L. Jackson, PhD
Senior Director of Research
miRagen Therapeutics, Inc.

Translating PD Biomarkers from Preclinical Studies to Clinical Trials: MRG-201, an Oligonucleotide Mimic of miR-29, Inhibits Collagen Expression, and Reduces Fibroplasia in Cutaneous Wounds

Corrie L Gallant-Behm, PhD, MQARS
Research Scientist III
Miragen Therapeutics, Inc.

Use of Biomarkers in the Development of RNAi Therapeutics

William Querbes, PhD
Director, Research
Alnylam

Panel Discussion

DAY TWO | THURSDAY, OCTOBER 26

12:00-1:30PM — **Round Table Discussion Luncheon, Exhibits, and Networking**

12:00-1:15PM

Luncheon Presentation

Japanese Perspective on the Preclinical Safety Assessment of Oligonucleotide Therapeutics

Session Chair
Arthur A. Levin, PhD
Executive Vice President, Research and Development
Avidity Biosciences

Representatives from Japanese regulatory and industrial joint working teams, including EWG members for ICH S6(R1), have discussed over the past two years the preclinical safety assessment of oligonucleotide therapeutics in comparison with biopharmaceuticals and low molecular new chemical entities. Unique perspectives will be shared with time for Q&A.

Japanese Initiative to Develop a White Paper for Oligonucleotide Therapeutics

Yoko Hirabayashi, MD, PhD
Division Head, Cellular Molecular Toxicology Center, Biological Safety and Research
National Institute of Health Sciences (NIHS), Japan

Study Design and Species Selection to Detect On-Target and Off-Target Effects

Kazushige Maki, DVM, PhD
Senior Scientist, Toxicology
PMDA, Japan

Lessons Learned from Biopharmaceuticals

Takahiro Nakazawa, PhD
CSO
AnGes, Inc., Japan

1:30-3:00PM

Session 7

Concurrent Breakout Sessions

TRACK A
Recently Approved and Late-Stage Oligonucleotide Drugs

Session Chair
G. Susan Srivatsa, PhD
President
ElixinPharma

This session will cover recent experience with approved and late-stage oligonucleotide drugs. The first presentation will address the CMC challenges associated with the review and approval of Nusinersen, and the second will cover regulatory experience with late-stage development of an siRNA drug. There will be a panel discussion that may include representatives from the FDA and BfArM.

SPINRAZA (nusinersen) Approval: CMC Strategies and Lessons Learned

Firoz Antia, PhD
Director, Technical Development
Biogen

CMC Strategies for Late-Stage Development of siRNA Oligonucleotides

Vidhya Gopalakrishnan, PhD
Senior Vice President, Pharmaceutical Development
Quark Pharmaceuticals, Inc.

Panel Discussion

Joining the speakers:

Olen Stephens, PhD
Chemist
CDER, FDA

Daniel Capaldi, PhD
Vice President, Analytical and Process Development
Ionis Pharmaceuticals, Inc

TRACK B/C
Predicting Clinical Safety from Nonclinical Data: Case Studies

Session Co-Chairs
Arthur A. Levin, PhD
Executive Vice President, Research and Development
Avidity Biosciences

Barbara Wilcox, PhD
Pharmacologist, OMPT, OND, ODEI, DNP
CDER, FDA

The most fundamental goal of toxicity studies is to predict the safety of drugs in clinical trials. This session will focus on some case-studies of how nonclinical data are being used to avoid adverse effects in clinical trials and how nonclinical data can be used to understand safety signals from clinical trials. In addition, the session features a discussion of the Agency's database of oligonucleotide therapeutics how the data are collected and being used.

Using Nonclinical Data to Interpret Clinical Safety Signals

John Vest, MD
Senior Director, Clinical Development
Alnylam Pharmaceuticals, Inc.

A Sensitive In Vitro Screening Approach to Assess the Hybridization-Dependent Toxic Potential of High Affinity Single Stranded Gapmer Oligonucleotides

Andreas Dieckmann, PhD
Senior Principal Scientist
F. Hoffmann-La Roche, Switzerland

Regulatory Application of a Nonclinical Database for Oligonucleotide Therapeutics at FDA

Xuan Chi, MD, PhD
Pharmacology/Toxicology Reviewer, Division of Cardiovascular and Renal Products, OND
CDER, FDA

Panel Discussion

3:00-3:30PM — **Refreshment, Exhibits, and Networking Break**

3:30-5:00PM

Session 8

Gene Editing: Driving CRISPR to the Clinic in Different Vehicles

Session Co-Chairs

Gerald Cox, MD, PhD
Chief Medical Officer
Editas

Iwen Wu, PhD
Team Leader of Pharmacology and Toxicology 1, Office of Tissues and Advanced Therapies (OTAT)
CBER, FDA

CRISPR is a powerful new technology whose genome editing versatility is being harnessed to usher in a new class of potential genetic therapies. While offering the promise of "one and done" treatments, human genome-based therapies also pose unique challenges for drug development. This session will examine two examples of early stage CRISPR-based medicines being developed to treat rare genetic diseases of the liver using systemic lipid nanoparticles and of the eye using subretinal delivery of AAV5. Preclinical evaluation of proof of concept, delivery, and specificity will be presented. As the CRISPR field evolves, so do the regulatory considerations regarding patient safety and risk-benefit. FDA's perspective and insights on preclinical data needed to support the transition of CRISPR-based medicines into the clinic will be discussed.

Robust In Vivo Gene Editing with Systemic Lipid Nanoparticle Delivery of CRISPR/Cas9 RNA Components

Amy Rhoden Smith, PhD
Principal Scientist
Intellia

Preclinical Development of AAV5 Encoding CRISPR/SaCas9 for the Treatment of Infantile Blindness Caused by Leber Congenital Amaurosis Type 10

Gerald F. Cox, MD, PhD
Chief Medical Officer
Editas Medicine, Inc.

Preclinical Considerations for Gene Therapy Products Involving Gene Editing Technology: An FDA Perspective

Ying Huang, PhD
Pharmacologist, Office of Tissues and Advanced Therapies
CBER, FDA

5:00-5:30PM

DIA Oligonucleotide Safety Working Group (OSWG) – Open Meeting

Attend to learn more or meet fellow members, hear about what's happening in the working group, and join in the latest discussions on the newest hot topics.

DAY THREE | FRIDAY, OCTOBER 27

7:00AM-12:00PM — **Registration**

7:00-8:00AM — **Continental Breakfast and Networking**

8:00-9:30AM — **Session 9**
Concurrent Breakout Sessions

TRACK A
Interactive Discussion of CMC Challenges and Moving Forward

Session Chair

Kim Tyndall
Director of CMC Regulatory Affairs
GlaxoSmithKline

During this session you will have the opportunity to interact with panelists to discuss current and future concerns in the development of oligonucleotide programs. This open discussion will focus on a set of questions and topics that have been predetermined prior to the conference and will include examples from case-studies as well as complications faced by regulators.

Panelists

Ramesh Raghavachari, PhD
Chief, Branch I, DPMA1, OLDP, OPQ
CDER, FDA

Ashley Boam, PhD
General Health Scientist
CDER, FDA

René Thürmer, PhD
Deputy Head of the Unit Pharmaceutical Biotechnology
BfArM - Federal Institute for Drugs and Medical Devices, Germany

TRACK B/C
Expanding Therapeutic Utility via Targeted Delivery

Session Co-Chairs

Patrik Andersson, PhD, ERT
Principal Scientist, Discovery Safety Specialist
AstraZeneca R&D, Sweden

Sree Rayavarapu, PhD
Toxicologist
FDA

This joint preclinical/clinical session will present novel translational insights of GalNAc-conjugated ASOs as well as novel targeting strategies for increasing productive uptake into cell types that normally are challenging to reach with oligonucleotide therapeutics. These include muscle and immune cells as well as pancreatic islets. The presentations will be followed by a 30 minute panel discussion.

Discussion topics include:

- Main utilities and obstacles of targeted delivery of oligos
- Specific regulatory considerations to targeting approaches

Translational Development of a GalNAC-Conjugated LNA-Based Single Stranded Oligonucleotide

Wouter Driessen, PhD, MS
DMPK Project Leader
F. Hoffmann-La Roche AG, Switzerland

Oligonucleotide Therapeutics Now on Target

Arthur A. Levin, PhD
Executive Vice President, Research and Development
Avidity Biosciences

Targeting Antisense Oligonucleotides to Pancreatic Islets

Patrik Andersson, PhD, ERT
Principal Scientist, Discovery Safety Specialist
AstraZeneca R&D, Sweden

Panel Discussion

9:30-9:45AM — **Refreshments and Networking Break**

DAY THREE | FRIDAY, OCTOBER 27

9:45-11:15AM

Session 10
Hot Topics in Oligonucleotide Therapeutics

Session Co-Chairs

Arthur A. Levin, PhD
Executive Vice President, Research and Development
Avidity Biosciences

Shwu-Luan Lee, PhD
Pharmacologist, OHOP, DHOT
CDER, FDA

As we learn more about RNA biology, its importance in the regulation of gene expression, and its role in disease processes, it is becoming clear there are many more ways to use oligonucleotides as therapeutic agents. With the identification of novel exploitable mechanism of RNA modulation, the range of diseases that can be targeted increases. This session will explore multiple novel ways to modulate RNA biology that may ultimately be used as a way to address disease processes and become the foundation for new therapeutic agents.

Antisense-Mediated Control of RNA Splicing to Treat Monogenic Diseases

Huw M. Nash, PhD
Chief Executive Officer
Stoke Therapeutics, Inc.

A to I Editing and Neuronal Plasticity

Joshua Rosenthal, PhD
Senior Scientist
The Marine Biological Laboratory, University of Chicago

A Site-Directed RNA Editing Strategy to Correct Genetic Mutations

Maria Montiel-Gonzalez, PhD
Post Doctoral Fellow
The Marine Biological Laboratory, University of Chicago

Stereodefined LNA Phosphorothioates: A New Perspective in RNA Therapeutics

Troels Koch, PhD, MSc
Vice President, Head of Research, RNA Therapeutics
Roche Innovation Center Copenhagen, Denmark

11:15AM-12:00PM

Closing Session
Panel Discussion

Session Co-Chairs

James Thompson, PhD
Head, CMC Project Management
Moderna Therapeutics

James Wild, PhD
Pharmacologist
CDER, FDA

This panel discussion is meant to highlight the challenges and issues with the development of oligonucleotide-based products in general, and as brought forth at this conference. The intention is to transform this discussion into action-oriented objectives to address the regulatory and industry issues and challenges affecting us all.

Panelists

Emily J. Place, PhD, MPH
Pharmacologist, Office of New Drugs
CDER, FDA

Arthur M. Krieg, MD
President and CEO
Checkmate Pharmaceuticals

Jeffery A. Engelhardt, DVM, PhD, DACVP, FIATP
Vice President, Pathology and Nonclinical Drug Safety
Ionis Pharmaceuticals, Inc.

Arthur A. Levin, PhD
Executive Vice President, Research and Development
Avidity Biosciences

Daniel Capaldi, PhD
Vice President
Analytical and Process Development
Ionis Pharmaceuticals, Inc

Kim Tyndall
Director of CMC Regulatory Affairs
GlaxoSmithKline

12:00PM

Conference Adjourned