Opportunities and Challenges: Generic Oligonucleotide Drugs

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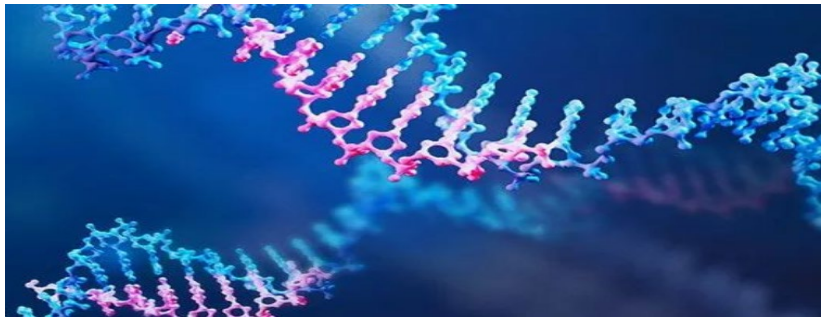
Any representation of brand name drugs in this talk are for purposes of scientific discussion and specific comparison.



Introduction

- Oligonucleotide drugs regulated by CDER as NDAs/ANDAs – chains of nucleic acid (approximately 20 to 40mer for currently approved drugs)
- Oligonucleotide pharmaceutics
  - Target specific genetic sequences for medical purposes
  - Rapid advances for biopharmaceutic therapeutics (and preventatives) for previously untreatable diseases
  - Wide range of target diseases – genetic disorders, cancer, viral infections
  - Potential for personalized medicine and rare disease

FDA Approved Oligonucleotide Drugs (2023)

Proprietary name	Active ingredient	Category	Length of Oligonucleotide	Approval Date
VITRAVENE	Fomivirsen sodium	Phosphorothioate ASO	21	August 26, 1998
MACUGEN	Pegaptanib sodium	Phosphate oligonucleotide aptamer	28	September 17, 2004
KYNAMRO	Mipomersen sodium	Phosphorothioate ASO	20	January 29, 2013
EXONDYS 51	Eteplirsen	Phosphorodiamidate morpholino ASO	30	September 19, 2016
SPINRAZA	Nusinersen sodium	Phosphorothioate ASO	18	December 23, 2016
ONPATTRO	Patisiran sodium	Double-stranded siRNA (LNP)	19+2 (antisense)	August 10, 2018
TEGSEDI	Inotersen sodium	Phosphorothioate ASO	20	October 5, 2018
GIVLAARI	Givosiran sodium	Double-stranded siRNA (GalNAc)	21+2 (antisense)	November 20, 2019
VYONDYS 53	Golodirsen	Phosphorodiamidate morpholino ASO	25	December 12, 2019
VILTEPSO	Viltolarsen	Phosphorodiamidate morpholino ASO	21	August 12, 2020
OXLUMO	Lumasiran sodium	Double-stranded siRNA (GalNAc)	21+2 (antisense)	November 23, 2020
AMONDYS 45	Casimersen	Phosphorodiamidate morpholino ASO	22	February 25, 2021
LEQVIO	Inclisiran sodium	Double-stranded siRNA (GalNAc)	21+2 (antisense)	December 22, 2021
AMVUTTRA	Vutrisiran sodium	Double-stranded siRNA (GalNAc)	21+2 (antisense)	June 13, 2022
QALSODY	Tofersen	Phosphorothioate ASO (gapmer)	20	April 25, 2023
IZERVAY	Avacincaptad pegol sodium	Phosphate oligonucleotide aptamer	39	August 4, 2023
RIVFLOZA	Nedosiran sodium	Double-stranded siRNA (GalNAc)	20+2 (antisense)	September 29, 2023
WAINUA	Eplontersen sodium	Phosphorothioate ASO (gapmer, GalNAc)	20	December 21, 2023

Approved Oligonucleotide Drug Indications

Proprietary name	Active ingredient	Clinical Indication
VITRAVENE	Fomivirsen sodium	CMV retinitis in AIDS patients
MACUGEN	Pegaptanib sodium	Age-related macular degeneration
KYNAMRO	Mipomersen sodium	Homozygous familial hypercholesterolemia to reduce LDL-C, apo-B, and T cholesterol
EXONDYS 51	Eteplirsen	Duchenne muscular dystrophy exon 51 skipping
SPINRAZA	Nusinersen sodium	Spinal muscular atrophy (survival motor neuron anti-sense)
ONPATTRO	Patisiran sodium	Hereditary transthyretin amyloidosis polyneuropathy
TEGSEDI	Inotersen sodium	Hereditary transthyretin amyloidosis polyneuropathy
GIVLAARI	Givosiran sodium	Acute hepatic porphyria
VYONDYS 53	Golodirsen	Duchenne muscular dystrophy exon 53 skipping
VILTEPSO	Viltolarsen	Duchenne muscular dystrophy exon 53 skipping
OXLUMO	Lumasiran sodium	Primary hyperoxaluria type 1 to lower urinary and plasma oxalate
AMONDYS 45	Casimersen	Duchenne muscular dystrophy exon 45 skipping
LEQVIO	Inclisiran sodium	Heterozygous familial hypercholesterolemia and primary hyperlipidemia
AMVUTTRA	Vutrisiran sodium	Hereditary transthyretin amyloidosis polyneuropathy
QALSODY	Tofersen	Amyotrophic lateral sclerosis
IZERVAY	Avacincaptad pegol sodium	Advanced dry age-related macular degeneration – geographic atrophy
RIVFLOZA	Nedosiran sodium	Primary hyperoxaluria type 1 to lower urinary oxalate
WAINUA	Eplontersen sodium	Hereditary transthyretin amyloidosis polyneuropathy

Potential Benefits

- Many of the oligonucleotide products have been approved for rare orphan diseases
- Some oligonucleotide drug products have been approved on the basis of surrogate endpoints
- See individual labeling for point estimates of effect – which can vary

Safety and Toxicity – Generic Concerns

- Just as with peptides, the key generic safety concerns arise from any differences to the reference listed drug.
- Potential for unwanted immune response and general (including hepatic and renal) toxicities – how similar is impurity profile?
- Potential for off-target effects (failure to target or API impurity, differences in delivery of product, including device constituent)
- Unknown long-term effects – may be difficult to ascertain due to inter-product switching

Practical Challenges for Generics

- API characterization
- Obtaining Reference Drug
- Immunogenicity
- Delivery and Stability
- Manufacturing scalability

Drug Product Sameness & Impurities

- Differences can result from
  - API synthesis – all oligonucleotide drugs are synthetic by nature
  - Chirality and diastereomers
  - API purification
  - Excipient impurities
  - Degradation (in process vs. storage)

Generic Drug Development

- Generic drug statutes and regulations apply to products that aim to be copies of NDA oligonucleotide drugs
- FDA is committed to providing a clear pathway for generic drugs to ensure access to quality drugs for the American public
- There currently are no ICH or FDA guidelines that specifically address the quality aspect and expectations for oligonucleotide drugs

Product-Specific Guidances (PSGs)

- To assist generic drug development, FDA develops product-specific guidances for each reference listed product, including many complex drug products such as oligonucleotide drugs.
- To date, FDA has developed 13 PSGs towards oligonucleotide drug products with more on the way.

Pre-ANDA Development

- FDA offers routes for direct advice in developing an ANDA submission including
  - Controlled Correspondence – for specific questions related to quality or bioequivalence
  - Pre-development (PDEV) pre-ANDA meetings to propose alternative approaches from what is discussed in the PSG or if there is not a PSG

Future Tools

- Known unknowns:
  - Impact of impurities on safety
- Tool Development Needs
  - Advanced analytical methods
  - Sensitive assays
  - Immunogenicity Models

Thank You

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