Developing Product-Specific Guidances on Oligonucleotides for Generic Drug Development

7th USP Workshop on Therapeutic Peptides and Oligonucleotides

February 28, 2022

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Outline

- Introduction: oligonucleotide-based therapeutics
- Generic drug development: regulatory considerations
- Developing product-specific guidances on oligonucleotides
- Summary

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Oligonucleotide-Based Therapeutics

- Oligonucleotides: Nucleic acid polymer chains that can act in a sequence specific manner to control gene expression
- Therapeutic oligonucleotides exert their effect through suppression of, or interference with mRNA translation, immune stimulation, protein binding, or through induction of exon skipping
- Therapeutic oligonucleotides can target a broad range of mRNAs (encode all cellular proteins) including those protein targets considered “undruggable” by small molecule or protein therapeutics

Oligonucleotide-Based Therapeutics

- Oligonucleotide-based therapeutics include:
  - Antisense oligonucleotides (ASOs)
  - Small interfering RNAs (siRNAs)
  - Small hairpin RNAs (shRNAs)
  - Anti-micro RNAs (anti-miRNAs)
  - Aptamers
  - Others (messenger RNAs, etc.)
- Synthetic oligonucleotides: Are regulated as drugs by CDER, FDA
- Vector-based or promotor-driven oligonucleotides: Are regulated as biologics by CBER, FDA

FDA Approved Synthetic Oligonucleotide Drugs

Proprietary name	Active ingredient	Category	Length of Oligonucleotide
VITRAVENE	Fomivirsen sodium	Phosphorothioate ASO	21
MACUGEN	Pegaptanib sodium	Phosphate oligonucleotide aptamer	28
KYNAMRO	Mipomersen sodium	Phosphorothioate ASO	20
EXONDYS 51	Eteplirsen	Phosphorodiamidate morpholino ASO	30
SPINRAZA	Nusinersen sodium	Phosphorothioate ASO	18
ONPATTRO	Patisiran sodium	Double-stranded siRNA	19+2 (antisense)
TEGSEDI	Inotersen sodium	Phosphorothioate ASO	20
GIVLAARI	Givosiran sodium	Double-stranded siRNA	21+2 (antisense)
VYONDYS 53	Golodirsen	Phosphorodiamidate morpholino ASO	25
VILTEPSO	Viltolarsen	Phosphorodiamidate morpholino ASO	21
OXLUMO	Lumasiran	Double-stranded siRNA	21+2 (antisense)
AMONDYS 45	Casimersen	Phosphorodiamidate morpholino ASO	22
LEQVIO	Inclisiran	Double-stranded siRNA	21+2 (antisense)

Antisense Oligonucleotide Drugs

- Antisense oligonucleotides (ASO) are small pieces of synthetic oligonucleotides, generally 12-30 nucleotides in length that can bind to specific molecules of RNA by Watson-Crick base pairing rules
- We will focus mainly on ASO, but the discussions are generally applicable to siRNAs

Regulatory Challenges on Oligonucleotides

- No ICH* or FDA guidelines that specifically address the quality aspect/expectations for oligonucleotide drugs
- No consensus on impurity reporting, identification and qualification thresholds
- Impurity characterization:
  - Most impurities exist as mixtures of closely related molecules
  - Many impurities coelute with the active ingredient
  - Lack of analytical methods to adequately resolve impurities
- Additional challenges for generic oligonucleotide drug development

*ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Generic Drugs

A generic drug is a ‘copy’ of the name-brand product, the reference listed drug (RLD). A generic drug must demonstrate, among other things, it is therapeutically equivalent* to the RLD.

- **Pharmaceutical equivalent (PE)**
- Bioequivalent (BE)
- Can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling
- Adequately labeled
- Manufactured in compliance with cGMP regulations

*For definition, see 21 CFR 314.3(b)

cGMP: current Good Manufacturing Practice

Generic Drugs and API Sameness

To be pharmaceutical equivalence*, a drug product must:

- **Contains identical amounts of the same active pharmaceutical ingredient (API) as the RLD**
- Uses same dosage form (e.g., solution) and route of administration (e.g., injection)
- Meets the same compendial standards for strength, quality, purity, and identity including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates

<u>API sameness is a requirement for generic drugs</u>

* For definition, see 21 CFR 314.3(b)

Generic Drugs and Bioequivalence

Bioequivalence* (BE) is defined as:

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar experimental conditions
  - Most ASO drugs are parenteral solutions for injection, BE may be considered self-evident and can be waived per 21 CFR 320.22(b)(1)**

*For definition, see 21 CFR 314.3(b)

**To be eligible for a waiver of in vivo BE testing a generic drug should contain same active ingredient and inactive ingredients and in the same concentration as the reference listed drug

Keys for Generic ASO Development

- Demonstrating API sameness
- Comparative impurities analysis (product-related impurities and other impurities) including information to justify that any impurity differences in the generic do not give rise to unknown differences in:
  - Immunogenicity
  - Toxicity

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Product-Specific Guidances

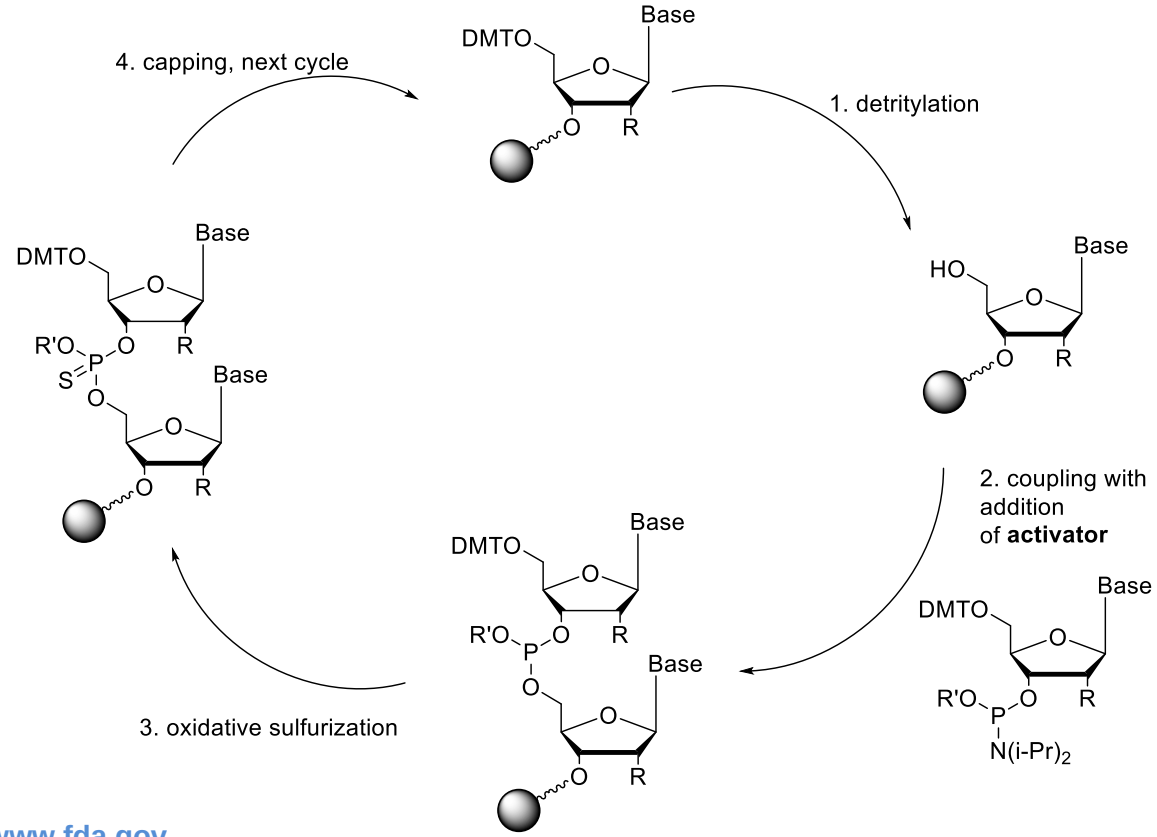
- Started in 2007, product-specific guidances (PSGs) provide the Agency's current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to a specific reference listed drug
  - PSGs are posted on a quarterly basis and as of January 2022, there are 1,949 posted PSGs.[1]
  - In GDUFA II (FY 2018-2022), FDA committed to posting a PSG for complex products as soon as scientific recommendations are available.[2]
  - For GDUFA III (FY 2023-2027), FDA has proposed to posting a PSG for complex products, 50% two years after NDA approval and 75% three years after NDA approval.[3]
- Developing PSGs for oligonucleotides will be critical for generic oligonucleotide drug development

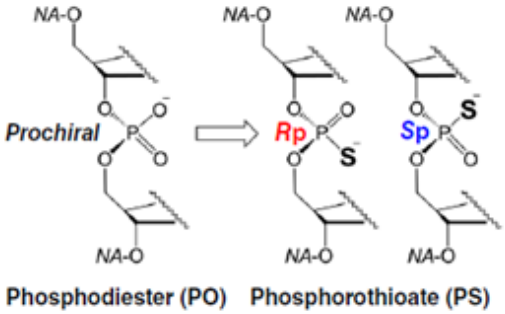
1. FDA Website: Product-Specific Guidances for Generic Drug Development (https://www.accessdata.fda.gov/scripts/cder/psg/)
2. GDUFA II commitment letter (https://www.fda.gov/media/101052/download)
3. GDUFA III commitment letter (https://www.fda.gov/media/153631/download)

Key Considerations in PSG Development

- API sameness recommendations
- Considerations on impurity profile assessment
  - — product-related impurities
  - — immunogenicity risk assessment

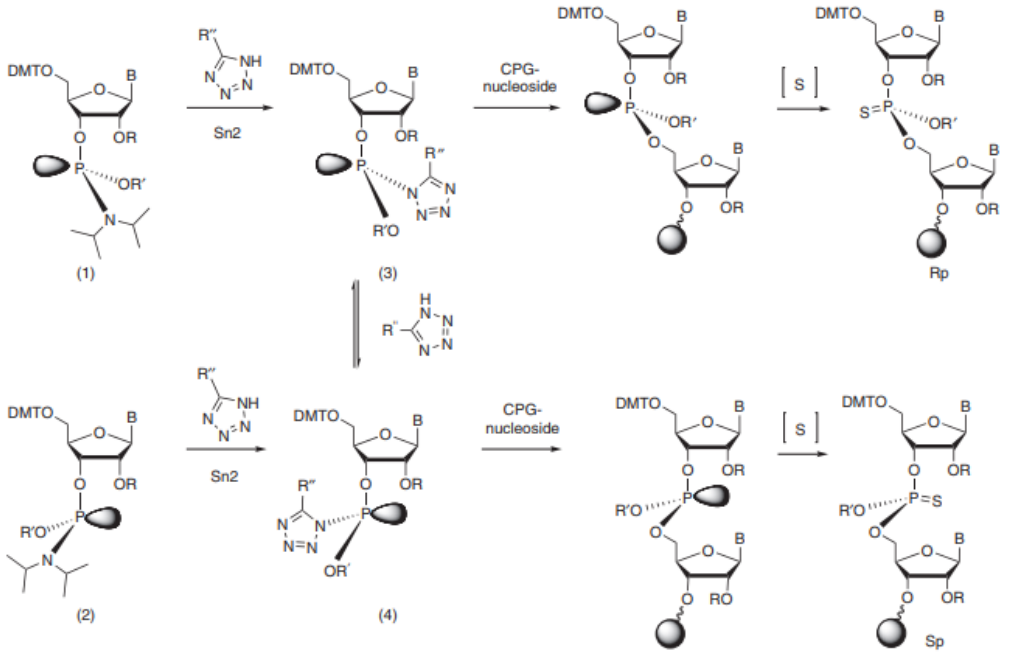
Solid Phase Synthesis of PS Oligonucleotides





PS: phosphorothioate

Solid Phase Synthesis of PS Oligonucleotides



- The product diastereomeric ratio is independent of the starting material configuration
- Activators affect the product diastereomeric ratio

Adapted from Jahns H et al *Nat Comm*, 2015, 6, 6317

Considerations for API Sameness

1. Equivalence in primary sequence, chemical structure and diastereomeric composition
   - Phosphorothioate (PS) stereochemistry affects pharmacologic properties of ASO*
   - Reaction conditions including activator selection affect PS stereochemical outcomes during ASO synthesis**
   - Employ a broad range of orthogonal analytical methods with sufficient sensitivity, discriminating and resolving power

*Iwamoto N, et al *Nat Biotechnol*. 2017, 35(9), 845-851
**Ravikumar V et al *Org. Proc. Res. Dev*. 2002, 6(6), 798-806

Characterization of Oligonucleotides

- Possible analytical methods/tools to explore:
  - Mass spectrometry (MS), including tandem MS (MS/MS)
  - Nuclear magnetic resonance (NMR) spectroscopy (^{1}H, ^{13}C and ^{31}P)
  - Liquid chromatography (LC)
  - Duplex melting temperature to a complementary strand

Considerations for API Sameness

2. Equivalence in physicochemical properties
   - Including aggregation state or higher order structure of the API in the product

Comparison of Characterization: Synthetic Peptides vs Oligonucleotides

Peptides	Oligonucleotides
Primary sequence, amino acid composition	Primary sequence, chemical structure and diastereomeric composition
Physicochemical properties, secondary structure, oligomers/aggregation states	Physicochemical properties to include aggregation state or higher order structures
Biological activities (in vitro and/or animals)	
Impurities (product-related and other impurities)	Impurities (product-related and other impurities)

Use orthogonal analytical methods

Evaluation of Impurities

Information to ensure impurities in the proposed generic oligonucleotide product will not alter the safety (including the immunogenicity) and efficacy compared to the RLD product

- Oligonucleotides are complex drug products.[1] Applicants should consider contacting the Office of Generic Drugs (OGD) (e.g., Pre-ANDA meeting) for questions related to generic oligonucleotide development including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the proposed generic product.

1. GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

Impurities: Things to Consider

- Impurity characterization:
  - Use of a range of suitable orthogonal methods for analyzing impurities, including those co-eluting with the API
  - If impurity levels can be controlled at or below those in the RLD
  - Criteria and justification for grouping impurities
- Immunogenicity risk assessment
  - Local inflammation and/or thrombocytopenia
  - Immunomodulatory effect

Summary

- Oligonucleotides are a class of new therapeutics that offer promising treatment solutions to a broad range of diseases. They also present unique scientific and regulatory challenges
- Office of Generic Drugs (OGD) is developing product-specific guidances on oligonucleotides to facilitate the generic development of oligonucleotide drug products
- OGD encourages applicants to contact OGD on questions related to generic oligonucleotide drug development, including questions on immunogenicity/inflammation risk assessment and impurity assessment

Acknowledgement

Office of Generic Drugs

Rob Lionberger
Lei Zhang
Darby Kozak
Yan Wang
Utpal Mondal

Office of Pharmaceutical Quality

Andre Raw
Bing Cai
Pahala Simamora
Cameron Smith
Likan Liang
Mohan Sapru
Kui Yang
Yili Li
Daniela Verthelyi

FDA Oligonucleotide Working Group (WG) Members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ADMINISTRATION