

Review of Synthetic Oligonucleotides by NIH/RAC

Opinion/Response of the Oligonucleotide
Safety Working Group (OSWG)

**NIH Public Hearing
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Oligonucleotide Safety Working Group (OSWG)

- Formed in 2007 following the 1st DIA (Drug Information Association) Oligonucleotide-based Therapeutics Conference
- Includes representatives from regulatory agencies (FDA, Health Canada, BfArM) and > 70 pharmaceutical companies
- Focus is on developmental aspects of short synthetic oligonucleotides
 - ❑ Includes antisense, siRNAs, aptamers, immunostimulatory oligonucleotides
- Open, inclusive membership with no restrictions

Objectives and Activities

- To share information, facilitate dialog and enable discussion on safety issues (observed and anticipated) in the development of short synthetic oligonucleotides as drugs
- Monthly meetings of sub-committees to discuss safety issues, including
 - ❑ Exaggerated pharmacology
 - ❑ Off-target effects
 - ❑ Genetic toxicology
 - ❑ Immune modulation
 - ❑ Impurities in drug substance and drug product
- Reflects current thinking of companies and regulatory authorities on issues
- Activities include:
 - ❑ Organization of DIA oligonucleotide-based therapeutics conferences (3 to date)
 - ❑ In the process of generating “white papers” by various sub-committees for publication
 - ❑ In 2008, successfully justified exclusion of synthetic oligonucleotides from definition of Advanced Medicinal Products (e.g. gene therapy) as proposed by the European Commission
 - ❑ Actively involved in responses to NIH proposal regarding RAC review of clinical protocols for synthetic oligonucleotides

Role of OSWG in Current RAC Issue

Time frame	Activity
May 2009	Responses sent by OSWG (and several member companies) to the 4 March 2009 Federal Register Notice
June 2009	Active participation (including representation on the panel) by members at NIH public hearing on 22 June 2009
September 2009	Provided definition of synthetic DNA and RNA oligonucleotides for exemption from RAC review of clinical trial protocols
December 2009	Following the NIH announcement exempting DNA oligonucleotides and not RNA oligonucleotides, OSWG communicated lack of scientific basis for the distinction, and requested exemption of RNA oligonucleotides
January to April 2010	Additional interactions by individual members with NIH to reiterate exemption of RNA oligonucleotides from RAC review
May 2010	OSWG proposal to RAC in response to NIH request for periodic review of clinical safety data of RNA oligonucleotides

Definition* for Synthetic Oligonucleotides For Exemption from RAC Review

Synthetic DNA or RNA oligonucleotide molecules with the following characteristics should be exempt:

- < 100 base pairs; AND
- Non-integrative; AND
- Non-replicative; AND
- Cannot function as a gene; AND
- Cannot be translated; AND
- Have a transient effect

*For ease of presentation, detailed definition presented to RAC has been simplified

Exemption for Synthetic RNA Oligonucleotides

Rationale

- Synthetic RNA oligonucleotides do NOT have the liabilities of classic recombinant molecules
- Synthetic oligonucleotides have been in clinical trials for > 20 years under the jurisdiction of FDA's CDER, with no significant or unexpected safety issues
- No scientific basis for exempting DNA and not RNA oligonucleotides
 - ❑ Both DNA and RNA oligonucleotides have a similar mechanism of action, i.e. they target mRNA, and do not impact the genome
 - ❑ Most antisense drugs in current development are DNA-RNA hybrid molecules
 - ❑ Further, modifications used with synthetic DNA oligonucleotides blur clear lines of distinction between DNA and RNA oligonucleotides
 - ❑ Effects are transient, and reversible upon cessation of dosing with DNA and RNA oligos
- Synthetic oligonucleotides are not unlike small molecules in their overall impact on cell systems; non-specific effects are known to occur
- **Synthetic DNA or RNA oligonucleotides delivered and/or expressed with use of viral vectors (e.g. shRNAs) are NOT sought to be exempt from RAC review**

Experience with European Commission Objection to Classification of Synthetic Oligonucleotides As Advanced Medicinal Products

Time frame	Activity
June 2008	<p>In response to the 8 April 2008 proposal by the European Commission to amend Annex I to Directive 2001/83/EC to include synthetic oligonucleotides as Advanced Therapy Medicinal Products, letters of objection sent by:</p> <ul style="list-style-type: none">• OSWG• Several companies• Concerned scientists led by Dr. Philip Sharp of MIT (signatories included Drs. David Baltimore of CalTech, Peter Gruss of Max Planck Institute, Craig Mello of UMass Medical, Paul Nurse of Rockefeller University, Harold Varmus of Memorial Sloan-Kettering, and Ernst-Ludwig Winnacker of the European Research Council)
September 2009	<p>Revised Directive issued by the EC excluding synthetic oligonucleotides from the definition of Advanced Medicinal Products</p>

OSWG Recommendation

- Exemption of synthetic RNA oligonucleotides from RAC review of clinical trial protocols
- Ideally not require any additional oversight from NIH/RAC

OSWG Proposal

In Response to NIH/RAC Request for Sharing of Clinical Safety Data of Synthetic RNA Oligonucleotides

1. Request active NIH/RAC participation at conferences:
 - DIA Oligonucleotide-based Therapeutics Conference (development focused; CMC and safety issues discussed, updates on clinical status of various molecules)
 - TIDES meetings (CMC focus; however, nonclinical and clinical issues also discussed)
 - OTS meetings (research oriented)
2. Provide NIH/RAC with “white papers” generated by OSWG subcommittees that reflect current thinking on safety-related issues in the development of synthetic oligonucleotides as therapeutics
3. Several companies developing synthetic RNA-based oligonucleotides have agreed to share safety data from completed clinical studies perhaps at an annual meeting to be organized by NIH

The OSWG looks forward to a mutually acceptable resolution to this issue



Acknowledgements

**Thanks to all members of the
OSWG for their active
participation and critical input
during this process**

Thank you

Definition for Synthetic Oligonucleotides

For Exemption from RAC Review

- Contain fewer than 100 nucleotides in total (single stranded, double stranded, or partially double stranded); AND
- Unable to integrate into the genome (i.e. do not contain known viral vector, transposable element or other known sequences designed to promote integration of the molecule into the genome) AND
- Cannot be replicated in cells (i.e. do not contain elements known to interact with DNA or RNA polymerase); AND
- Do not comprise a gene (i.e. do not contain promoter/enhancer elements, transcription initiation elements or polyadenylation sequences designed to enable the molecule to be transcribed into mRNA); AND
- Cannot be translated into protein (i.e. do not contain a 5' cap structure or internal ribosome entry site); AND
- Have a transient effect that is generally related to persistence of the oligonucleotide and/or an oligo-protein complex (i.e. the effect is reversible in time depending on the target and oligonucleotide stability and/or stability of the oligo-protein complex interaction, such that the effect is not permanent and the oligonucleotide must be re-administered to sustain the effect).