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EU Regulators' experience with synthetic oligonucleotides and mRNA technology

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EMA Regulatory and scientific virtual conference on RNA-based medicines
Session 2: Application of RNA technologies: CMC Opportunities and Challenges
2nd February 2023

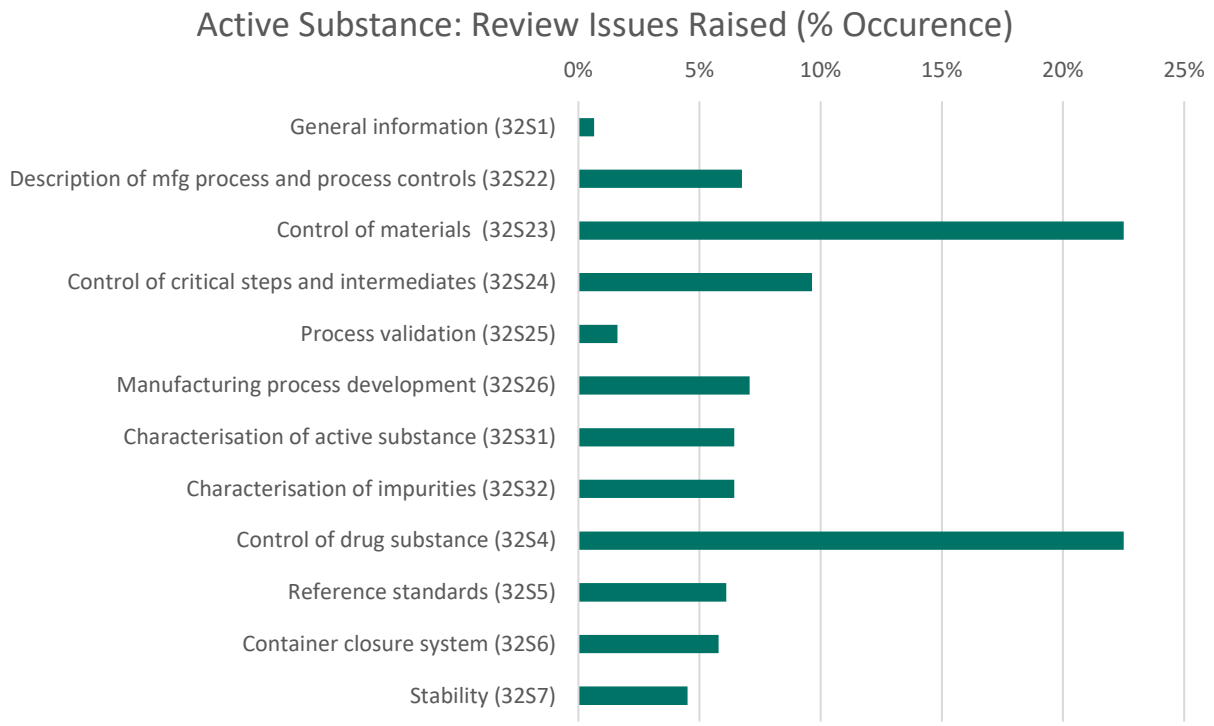
Disclaimer

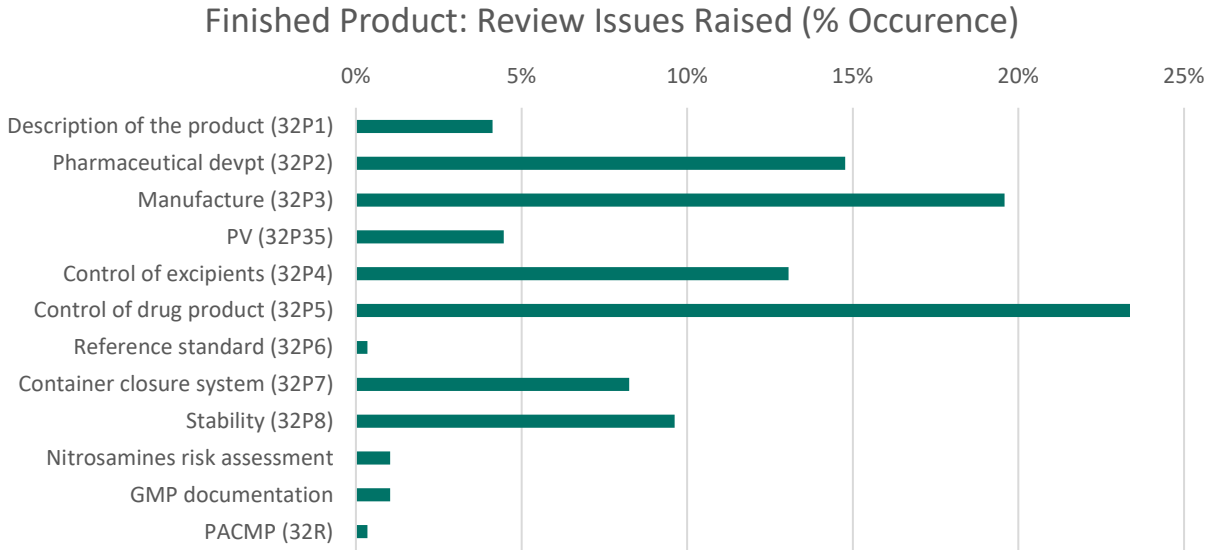
The views expressed in this presentation are those of the speaker and do not necessarily represent those of the BfArM and other European Regulatory Agencies.

Overview on MAAs (Synthetic Oligonucleotides)

Brand name	INN	MAH	MoA	Status
Vitravene	Fomiversen	Novartis Ophthalmics Europe Ltd	ASO	Withdrawn
Macugen	Pegaptanib sodium	PharmaSwiss Ceska Republika sro	Aptamer	Withdrawn
Genasense	Oblimersen	Genta development	ASO	Refused
Kynamro	Mipomersen	Genzyme Europe BV	ASO	Refused
Kyndrisa	Drisapersen	BioMarin International Ld	ASO	Withdrawn
Exondys	Eteplirsen	AVI Biopharma International Ltd	ASO	Refused
Spinraza	Nusinersen	Biogen Netherlands B.V.	ASO	Approved
Onpattro	Patisiran	Alnylam Netherlands B.V.	siRNA	Approved
Tegsedi	Inotersen	Akcea Therapeutics Ireland Ltd	ASO	Approved
Waylivra	Volanesorsen	Akcea Therapeutics Ireland Ltd	ASO	Approved
Givlaari	Givosiran	Alnylam Netherlands B.V.	siRNA	Approved
Oxlumo	Lumasiran	Alnylam Netherlands B.V.	siRNA	Approved
Leqvio	Inclisiran	Novartis Europharm Ltd	siRNA	Approved
Amvuttra	Vutrisiran	Alnylam Netherlands B.V.	siRNA	Approved
N/A	Tofersen	Not in public domain	ASO	Under evaluation

Review Issues (2017 – 2022, n = 9)





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EMA Guideline on the Development and Manufacture of Synthetic Oligonucleotides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/CHMP/QWP/735423/2022
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

A second concept paper on the establishment of a Guideline on the Development and Manufacture of Synthetic Peptides has been published. There are numerous similarities between synthetic peptides and oligonucleotides, however also fundamental differences. Therefore it has been decided to develop two separate guidelines.

Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

Agreed by Quality Working Party	29 June 2022
Adopted by CHMP for release for consultation	15 September 2022
Adopted by CVMP for release for consultation	8 September 2022
Start of public consultation	20 September 2022
End of consultation (deadline for comments)	20 December 2022

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Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- Synthetic oligonucleotides are at the interface of small molecules and biologicals and, from a quality point of view, specific considerations apply to this class of therapeutics
- The guideline will cover antisense and other single strand products, double strand products as siRNA and as a third subclass aptamers

The proposed guideline will address the following:

- Development of an overall integrated control strategy to ensure consistent quality of synthetic oligonucleotides and the resulting medicinal products, based on relevant CQAs
- Requirements specific for the solid-phase synthesis manufacturing pathway including requirements on batch definition and the description of splitting, pooling and re-processing steps applied in the purification process
- Selection of starting materials including a criticality assessment of their impurity profiles
- Characterisation approaches including investigation of the drug substance impurity profile

Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- Purity control strategy: product-related impurities and process-related impurities; use of orthogonal purity methods, discussion of grouping strategies for impurities
- Differences in requirements between single strand, double strand and aptamer oligonucleotide products will clearly be outlined
- Oligonucleotides have potential to use prior knowledge and platform technologies. Recommendations on how to justify applicability of prior knowledge and platform technologies will be provided
- Requirements for conjugation (e.g. GalNAc, PEG-ylation, monoclonal antibodies, peptides, proteins) approaches will be addressed
- The proposed guideline will follow the structure of Module 3 and the Guideline on the Chemistry of Active Substances where relevant. Additionally, finished product considerations (e.g. choice of excipients, formulation & sterilisation aspects) relevant to formulations containing synthetic oligonucleotides will be addressed

Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- In contrast to synthetic peptides no purity limits are stated in the Ph. Eur. Monograph ‘Substances for pharmaceutical use’ for synthetic oligonucleotides. Establishing harmonised limits could be considered in this GL. However, additional discussions are needed as analytical methods and specific oligonucleotide type of products are not comparable per se. The public consultation may facilitate comments from different stakeholders in this regard
- Considerations for active substances that are in solution (i.e. not isolated) will be provided
- First applications for generic oligonucleotides will be submitted in the near future. Additional considerations regarding quality aspects may be applicable for such submissions including demonstration of comparability and will be covered in the guideline
- Initiatives for the development of personalised antisense oligonucleotides (either for one patient or a small group of patients) are currently on-going and may be considered in this guideline
- End of consultation phase: 20 December 2022

Public Consultation Outcome

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Extract of some Key Messages from Public Consultation

- Clear definition of scope (which molecule classes are within / without of the scope)
- International harmonisation
- No additional regulatory burden
- Consideration of white papers published by EPOC
- How to address mutagenic impurities?
- Discussion and requirements for specifications
- Several comments on analytical techniques
- Clarity on expectations for benefit-risk analysis for sterilization method selection (sterile filtration vs terminal sterilisation
- Discourage from trying to establish generic purity limits – these are too dependent on chemistry, sequence (even within the same chemistry) and method
- Phase-appropriate approaches to CMC development during clinical development

Manufacturing Process Development

- The majority of dossiers is in line with the expectations from ICH Q11 and ICH Q8
- Pharmaceutical development sections of Module 3 are usually of good quality
- DOE studies are usually performed in small scale to optimise the manufacturing process
- Identification of normal operating ranges (NORs), set points and proven acceptable ranges (PARs)
- Criticality assessment of process parameters and identification of critical process parameters (CPPs) for synthesis, purification (and annealing)
- Criticality assessment of quality attributes and justification how the attributes are controlled
- Definition, description and justification of overall control strategy

Starting Materials

- Starting materials are an important part of the overall control strategy
- Unique challenges for oligonucleotides
- Phosphoramidites are more complex than many small molecule APIs
- Phosphoramidites are accepted starting materials
- Complex sequences in development programmes → Complex chemistry and syntheses for starting materials
- Many development programmes with linkers/conjugates
- Justification should be in line with ICH Q11 Q&A (August 2017)
- Documentation of suppliers is expected / change of suppliers will result in a variation
- Short description of starting material manufacturing process
- Criticality assessment of impurity profile is essential for oligonucleotides
- Impurity profiles for phosphoramidites from different suppliers should be compared

Impurities

- Good understanding of impurity profiles has been demonstrated
- For process-related impurities depletion should be demonstrated
- Risk analysis and theoretical purging considerations may be an suitable approach, however, also analytical data are requested
- Genotoxic impurities need to be comprehensively discussed in the dossier
  - EPOC publication on the determination of purge factors (March 2022)
- Presence of nitrosamines should be controlled and kept as low as possible
  - Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (03 August 2020, EMA/409815/2020 Rev.14, updated 21 December 2022)
- For starting material impurities understanding of their criticality on API quality should be demonstrated
- For complex starting materials a sound justification based on science and ICH Q11 Q&A should be provided including the control of impurity profile and impurities which may impact the purity of the resulting drug substance
- Aggregation should be addressed in regulatory submissions

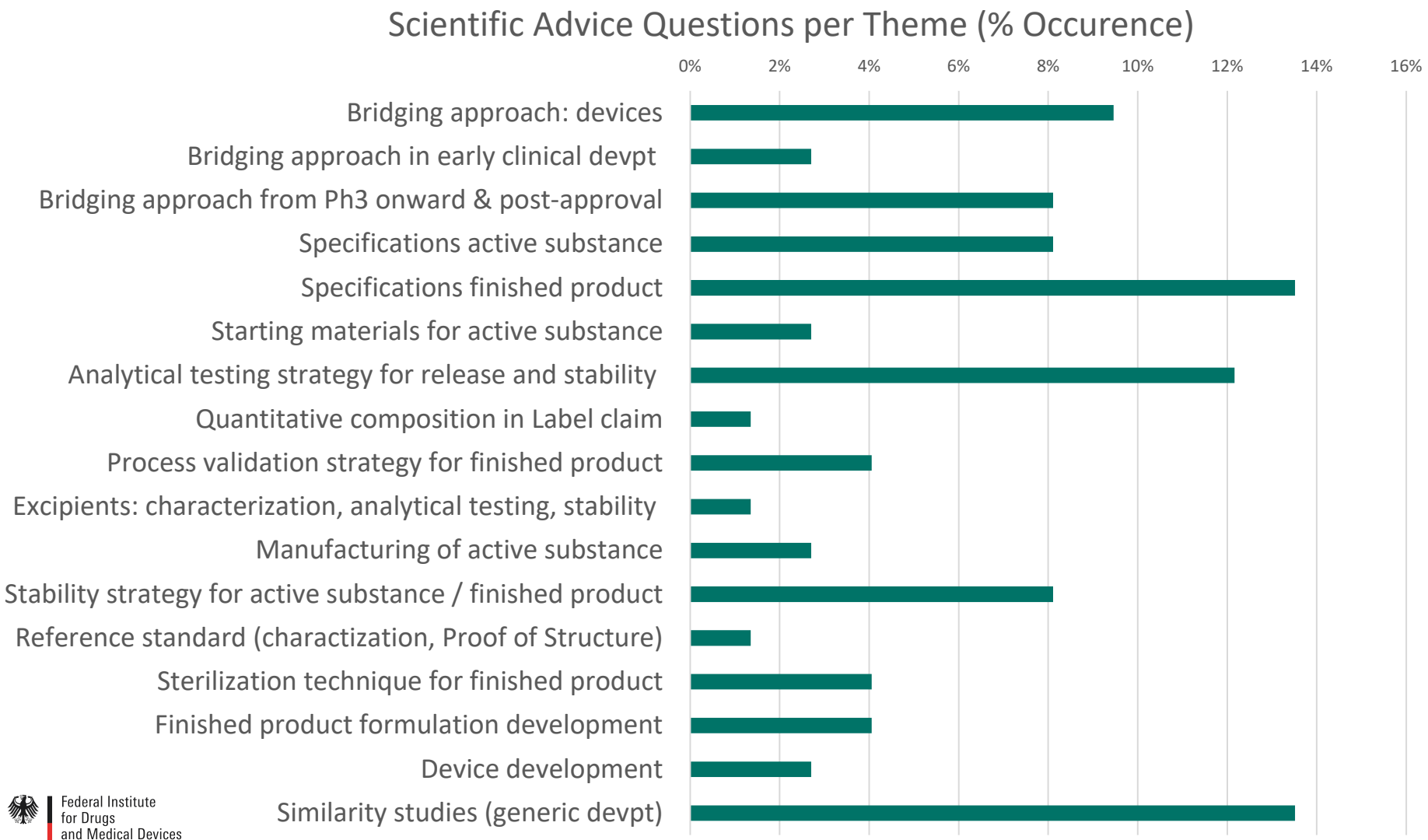
Specifications

- Unique challenges for oligonucleotide product-related impurities
- High quality analytical methods are pre-requisite
- Grouping strategy has to be justified by the applicant
- ‘Justification of specification(s)’ sections in Module 3 are extremely important
- Toxicological / clinical qualification is key
- Comparability studies during development using high quality analytical methods are requested
- Manufacturing process validation should show that commercial process result in a product that falls within clinically qualified limits
- Usually ± 3 x SD is adequate for setting of specifications
- Post-approval adjustment of specifications may be an option
- Early development batches should not be the basis on specification setting
- Differences between release and shelf-life specification for the drug product should be justified by data and knowledge of degradation pathways
- Specification attributes are very similar between the application procedures (see also EPARs)

Regulatory Trends

- Usually for antisense and siRNA molecules no bioassay is expected
- However, a justification for omission of bioassay should be provided
- Consistency of the distribution of stereo-isomers over variation in the synthesis process should be evaluated
- Not including routine tests on stereochemistry should be justified
- Process validation data for non-standard drug product manufacturing processes (sterile filtration) for full scale batches should be provided with submission
- Terminal sterilisation provides the highest assurance of sterility
  - EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container
- Decision trees for the selection of sterilisation methods is relevant for synthetic oligonucleotides
- Numerous scientific advice applications regarding this topic have been received recently. In numerous cases justification and provided/proposed data package is not considered sufficient!

Scientific Advice – Quality Questions (Synthetic Oligonucleotides)



11 Scientific Advice procedures with 51 quality questions in 2022 (6 procedures in 2021 with 23 questions)

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mRNA Therapeutics

- Limited experience for mRNA therapeutics
- However significant regulatory quality knowledge has been gained from the Covid19 mRNA vaccine applications
- Quality considerations for therapeutics and vaccines are similar
- Platform approaches are very likely
- Comparability considerations are important during development
- Consistency and robustness of the manufacturing process should be demonstrated
- Quality of materials and excipients is extremely relevant – Qualification of multiple suppliers
- Characterisation / Extended Characterisation vs. Routine Testing and Stability Testing
- Stability / Storage / Transportation
- Number of Scientific Advice Procedures is steadily increasing for a diverse type of products
- Main recurring questions in Scientific Advice Procedures are PPQ strategies, potency testing, analytical methods, and comparability
- First PRIME designations

mRNA Therapeutics

- Compendial methods as e.g. appearance, pH, osmolality, particulate mattter, sterility, bacterial endotoxins
- Identification
- Assay / Content
- Integrity / Purity
- Sequence
- Potency
- Capping efficiency
- Residual DNA template
- Residual dsRNA
- Delivery system testing (e.g. size and size distribution), encapsulation, release
- Lipid related tests (identity, content, impurities)

mRNA Therapeutics

- BWP Workplan for 2023 includes a proposal for a draft EMA guideline on quality of mRNA vaccines. Concept paper on this topic for public consultation is expected by mid-2023
- Guidance from other regions / organisations (e.g. WHO, USP)
- mRNAVAC WP has been established by EDQM (first F2F Meeting in February 2023)

Thanks to my EMA colleagues

Hilde Bastaerts

and Brian Dooley

Thank you very much for your attention!

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