# Leveraging Prior Knowledge to Support Early Phase Clinical Trial Applications:

## Regulatory CMC Considerations and Case Studies

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# Agenda

Concept and Regulatory Background

siRNA Platform Technology and Structural Similarity

Supportive Stability Data

Module 3 Structure

Response from Health Authorities

# Concept and Regulatory Background

## What is prior knowledge and how can it be leveraged in CMC development?

- Prior knowledge is the concept of taking the scientific knowledge from a similar product, modality, platform technology, or other aspect of process design and/or product quality controls and leveraging this knowledge in the development of a new medicinal product
- Use of prior knowledge has been established in multiple ICH guidance documents
  - ICH Guideline Q8 Pharmaceutical Development
  - ICH Guideline Q10 Pharmaceutical Quality System
  - ICH Guideline Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
- ICH guidances do not address how prior knowledge can be incorporated and structured within Module 3 Quality of the Common Technical Document (CTD) sections for regulatory submissions
- In 2022, Novo Nordisk RA and CMC teams selected two FIH clinical small interfering RNA (siRNA) assets to use prior knowledge in combination with long-term and accelerated stability data to propose shelf life

# Concept and Regulatory Background

## Prior knowledge to establish the shelf-life of an early phase investigational medicinal product

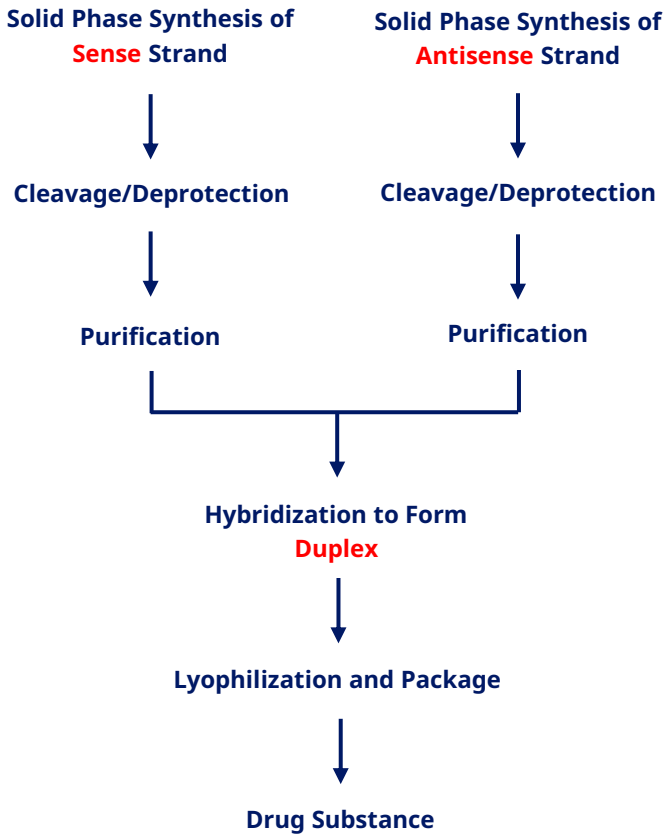
- Drug product stability data is generally critical path toward an FIH CTA submission
- Reduces the regulatory burden of submitting shelf-life extensions
- Reduces the re-labeling of drug products
- Reduces the risk of clinical trial material expiring prior to execution of the clinical study
- Reduces the risk of performing additional manufacturing with early phase/unoptimized processes and analytical methods

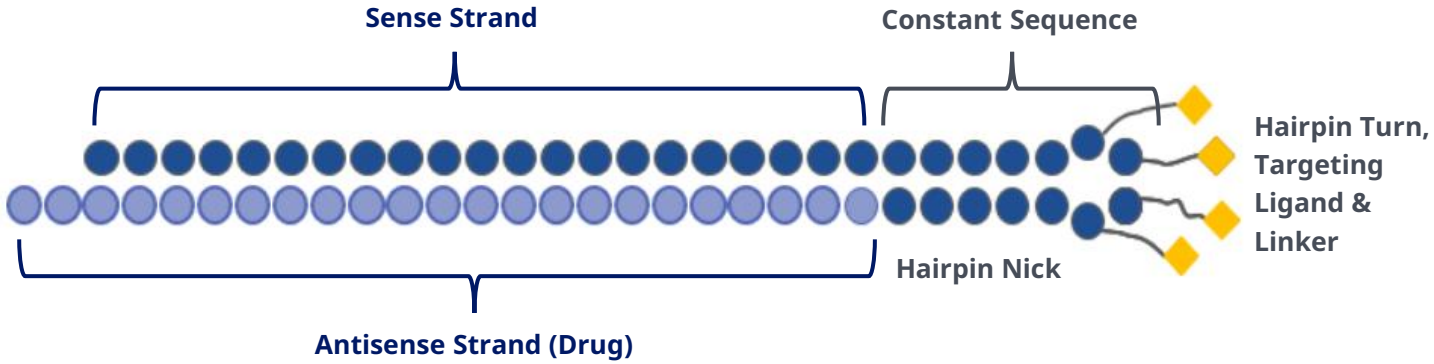
# siRNA Platform Technology and Structural Similarity

API SM Specifications

Single Strand Specifications (IPC)

Duplex (DS) Specification




## Drug Substance

Highly automated process
Synthesis via similar chemical transformations for each synthetic sequence
Similar drug substance starting materials and specifications
Similar in-process controls and drug substance release specifications
Similar impurity profile
Similar analytical procedures for purity determination

## Drug Product

Similar manufacturing process
Similar discriminating analytical methods
Similar in-process controls and release/stability specifications
Similar degradant profile
Risk based assessment for container closer systems and formulations

**Drug Product:** sterile liquid for S.Q. injection (e.g., reconstitution, pH adjustment, sterile filtration, vial filling/stoppering/over sealing)

# Supportive Stability Drug product data from early & late phase programs

## Stability data from three different phase 1–3 programs used to establish overall stability trends

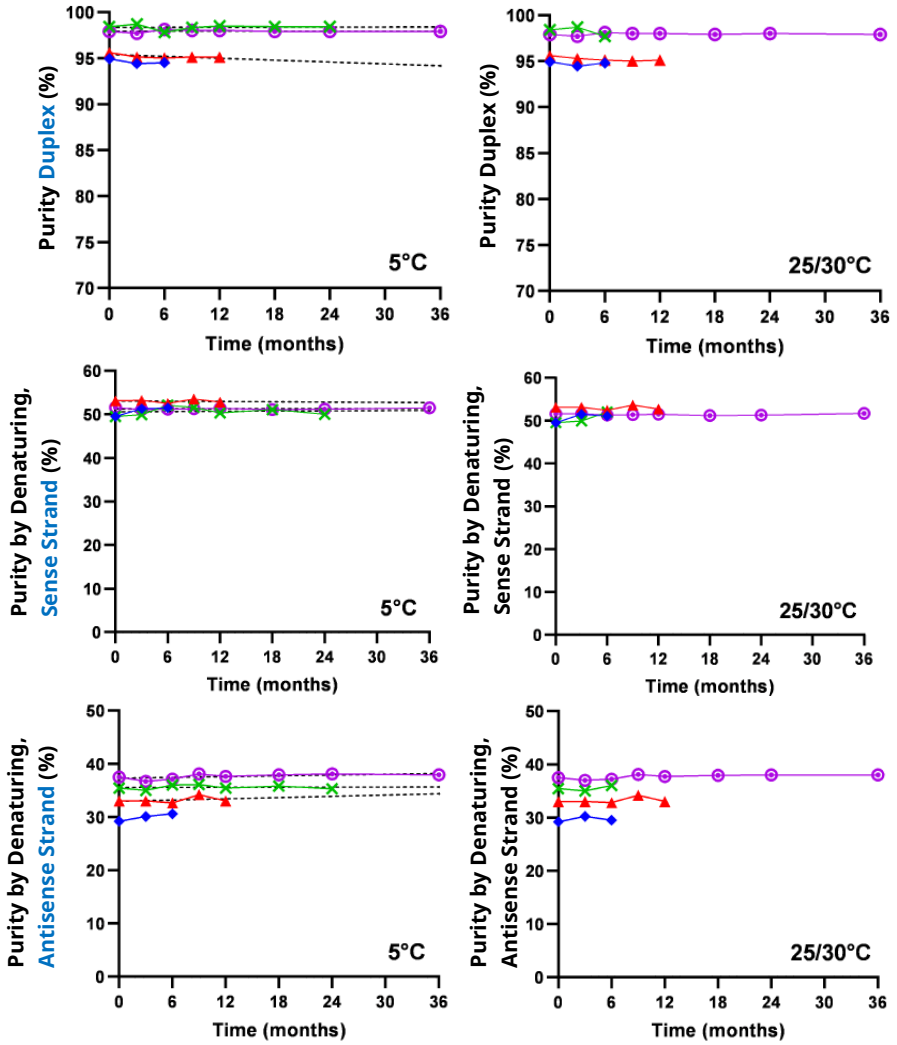
- Drug product A containing 36 months (M) at 25 °C, 36M at 5 °C, and 6M at 40 °C
- Drug product B containing 12M at 25 °C, 24M at 5 °C, and 6M at 40 °C
- Drug product C containing 12M at 25 °C, 12M at 5 °C, and 6M at 40 °C
- No significant change
- Forced degradation data (50 and 70 °C)

## Linear regression analysis was performed and extrapolated to 36M at the long term storage condition 5 °C

- All extrapolated slopes were found to be not significantly different from zero at a 95% confidence interval

## Investigational medicinal product stability data

- 6M at 25 °C, 6M at 5 °C, and 1M at 50 °C
- Forced degradation studies (70 °C)
- **Proposed CTA shelf life: 36M at 5 °C**



# **Module 3** Structuring prior knowledge within the CTD

In 2018, EMA published a meeting report regarding prior knowledge and its use in regulatory applications[1]

- Prior knowledge could be presented in supportive Module 3 Quality dossier sections (3.2.S.2.6, **3.2.P.2,** 3.2.A, 3.2.R)
- Where relevant, in Module 1 Regional Administrative Information [Scientific Advice letters, pre-submission meeting minutes (if appropriately flagged for assessor)]
- Prior knowledge needs to be visible and readily accessible to assessors in the application file and the underlying full data package should be available upon request
- A discussion of how the prior knowledge data is used should be integrated with the relevant product-specific data to provide an overall understanding of product development and control

[1] European Medicines Agency. *Meeting Report: Joint BWP/QWP Workshop with Stakeholders in Relation to Prior Knowledge and Its Use in Regulatory Applications*, November 2017, EMA/CHMP/BWP/187162/2018.

# **Module 3** Structuring prior knowledge within the CTD

Risk-based comparability assessments and supportive stability data from **drug products A–C** was submitted in **3.2.P.2 Pharmaceutical Development**

Section **3.2.P.8 Stability** essentially remained unchanged compared to a submission not leveraging prior knowledge

- 3.2.P.8 only presented stability data of the IMP (6M long term/accelerated) and proposed 36M shelf life
- 3.2.P.2 was referenced in 3.2.P.8 as part of shelf life justification
- If prior knowledge justification for 36M shelf life was not accepted, would only impact shelf life statement in 3.2.P.8 (3.2.P.2 and remainder of 3.2.P.8 not impacted and/or require re-authoring/re-submission)

# **Module 3** Structuring prior knowledge within the CTD

## Presentation of prior knowledge in 3.2.P.2 Pharmaceutical Development

| | |
|---|---|
| Overview of the siRNA **DS platform** | • Molecular structure diagram and structure matrix table comparing number of targeting ligands, 2´-O-methyl and 2´-deoxy-2´-fluoro subunits, number of phosphorothioate linkages, etc<br>• Comparative description of DS manufacturing process and control strategy |
| Overview of the siRNA **DP platform** | • Table comparing container closure system, formulation vehicle, formulation pH, target concentration |
| Presentation of **DP stability data** from **drug products A–C** | • Table of batches used in stability justification: drug product name, batch number, intended use of batch, and EudraCT or US CT.gov numbers/IMPD version number<br>• Summary of available stability data (e.g., storage conditions, time points, summary of analysis)<br>• Stability data and linear regression analysis |

# Response from Health Authorities

Two siRNA CTAs were submitted with the proposed 36M shelf life based upon 6M long-term/accelerated stability + prior knowledge data

CTAs were filed in European countries through national submissions (e.g., former EU Clinical Trial Directive 2001/20/EC)

| | |
|---|---|
| Country A | **Shelf life was accepted without any questions from HA** |
| Country B | Health authorities requested additional information<br>• justified controls for impurities based on the knowledge on the platform technology<br>• assessment of the potential impact of manufacturing the drug substance and drug product at different manufacturing sites<br>**These details were provided and the IMP 36 month shelf life was accepted** |

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For a recent publication describing this work, see:

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**ABSTRACT:** Prior knowledge was successfully used to support the clinical trial applications of two small interfering RNA (siRNA) investigational medicinal products (IMPs). A comparative, risk-based approach was used to introduce supportive stability data from three other siRNA IMPs to establish an initial 36 month drug product shelf life. The structuring of supportive data from other clinical programs into Module 3 Quality of the Common Technical Document and response from health authorities is additionally presented.