

Joint BWP / QWP workshop with stakeholders in relation to
prior knowledge and its use in regulatory applications

How to Use Prior Knowledge in Defining the Control Strategy

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EMA Prior Knowledge Workshop

Case Study: Oligonucleotide Control Strategy

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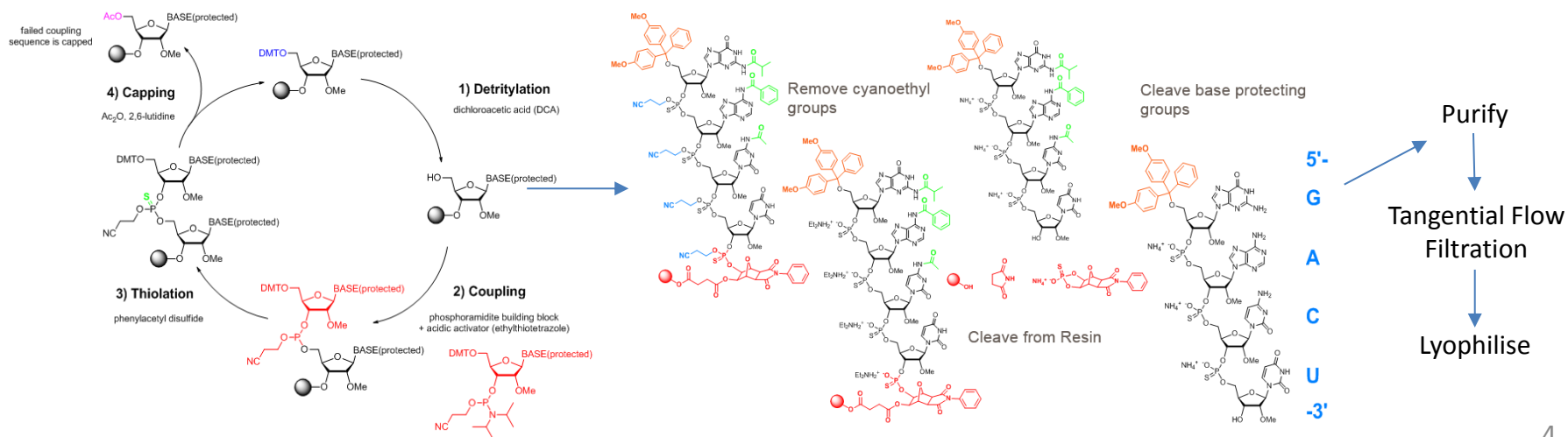
Introduction

- ❖ Oligonucleotides fall within the gap between “small molecule” and “BioPharm” compounds
- ❖ They are excluded from some ICH guidelines and there is limited guidance about manufacture or control
- ❖ The platform nature of therapeutic oligonucleotides and their manufacture means that there are many opportunities to exploit “prior knowledge”
- ❖ We propose that some of the control strategy of oligonucleotides could be “assumed” based on this prior knowledge, and standard controls, limits and risks could be standardised
- ❖ This case study will illustrate how prior knowledge of the manufacturing platform is used in the assessment of quality risks, to inform the development plan and deliver the control strategy

Oligonucleotide Manufacturing Platform

Platform manufacture – platform control

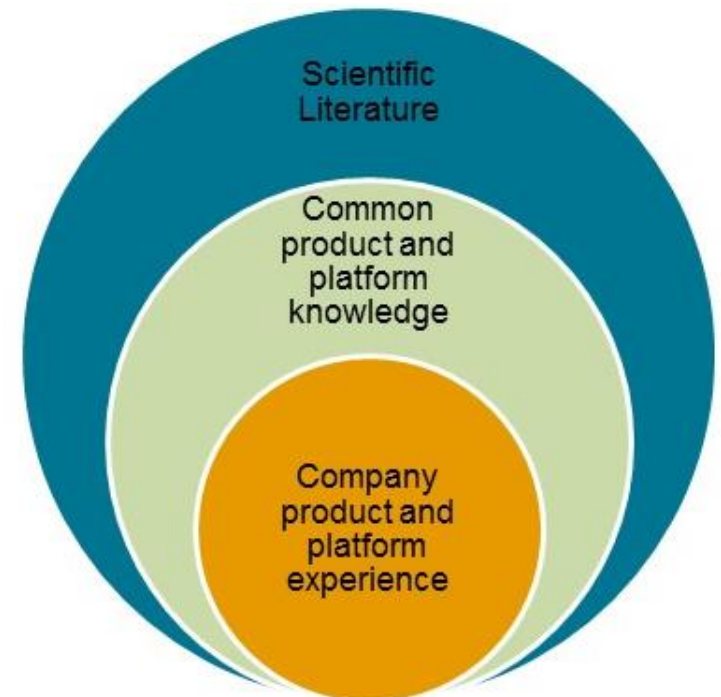
- Manufacture via a platform synthetic process applicable to multiple oligonucleotide products:
 - Highly automated process
 - Synthesis via similar chemical transformations for each synthetic sequence
 - Similar substrates, solubilities, kinetics, thermodynamics, mass transfer effects....
 - Scale is defined by available synthetic platforms (lab scale, commercial scale)
 - Equipment adaptations to support scale up from lab scale are the same each time
- Prior knowledge of the platform means consistent quality risks can drive consistent development strategies across multiple products



Utilising the Manufacturer's Prior Knowledge

- ❖ Only one oligonucleotide Applicant has internal commercial manufacturing capacity (although some more may invest)
- ❖ Commercial manufacture occurs at a limited number of expert CMOs
- ❖ CMOs have more extensive experience and prior knowledge than any individual Applicant

- Applicants utilise CMO's prior knowledge of their platform (subject to product specific confidentiality)
- This kind of prior knowledge sits between "*company product and platform experience*" and "*common product and platform knowledge*"
- It exceeds the applicant's product knowledge and experience but is not "common" knowledge as it is currently specific to the CMO



Populations of Impurities

- ❖ **Prior knowledge of chemistry principles** suggest that potential impurity groups are associated with a particular side reaction, which can form in any sequential cycle of the synthesis. Hence, the specific location in the sequence may differ, providing a “population” of similar impurities
- ❖ The individual impurities within these “populations” will have very similar (if not identical) mass, **chemical and physical properties** and **toxicological impact**
 - For example, the “N-1” population of impurities where a single nucleoside is missing from the sequence could contain up to 19 unique impurities, although more typically (due to repeating bases) contains 12-16 unique compounds
 - A second example is the “monophosphate” population of impurities, where a single thiolation step has failed resulting in an oxygen in place of a sulphur in a single position on the back bone – this population could contain 19 different impurities but they will all have identical mass.
- ❖ It is not possible to routinely analyse for each individual impurity within a population, nor is it considered quality critical
- ❖ **The concept of “populations” of impurities should be widely accepted, and not need to be justified within each submission and the control strategy should be based on this concept**

Safety of Potential Impurities

- ❖ Impurities “populations” found in therapeutic oligonucleotides typically contain only structural elements found in naturally occurring nucleic acids and the thus result in a low safety risk
 - A number of safety studies have been conducted demonstrating that impurities of similar length to the main compound do not have specific toxicological impact, only “class based” effects
 - Monophosphate impurities are widely known to have low toxicity
 - Whilst the argument that these impurities should be included in the active drug label claim has largely been disputed and it is generally agreed they should be controlled as impurities, it is evident they do not pose a safety concern
- ❖ Impurities classes which have previously been demonstrated to have no additional toxicological concern should not require additional non clinical safety studies.

Safe limits for full length, N-1 and N+1 impurities should be determined by dose ranging studies of the main compound rather than individual toxicological studies

Control of CQAs for Oligonucleotides

- ❖ Prior knowledge shows that, based on the nature of the manufacturing platform, **common classes of CQA** will occur across therapeutic oligonucleotides, and a common control strategy can be developed. With prior knowledge of the platform informing selection and control of the CQAs For example:
 - ❖ **Identity**
 - Due to the complex nature of oligonucleotide molecules, it is impossible to unequivocally identify the sequence by any single method. Patient safety can be assured by a combination of ID test and process controls – platform knowledge is used to inform these controls and risks
 - ❖ **Counter Ion Identification**
 - Identification through a specific and quantitative test for the counter ion should demonstrate that the correct counter ion is present and that the back bone is fully ionised (typically sodiated)
 - ❖ **Impurities**
 - Individual impurities should be controlled as populations
 - Limits for individual impurities should be based on dose ranging studies
- ❖ Control of CQAs through upstream parametric controls, based on prior knowledge and supported by appropriate experimental verification affords a practical control strategy

Overall Points for Discussion

Impact of prior and platform knowledge

- ❖ Utilisation of prior knowledge to inform platform risk assessments is key
- ❖ The prior knowledge of a CMO which spans across the manufacturing platform is likely to be more relevant than the applicant's prior knowledge
- ❖ Impurities should be considered and controlled as populations
- ❖ Impurities should be “qualified” with dose ranging studies rather than individual non-clinical studies
- ❖ A common control strategy could be employed for multiple oligonucleotide compounds
- ❖ Due to the complex nature of oligonucleotides, a practical control strategy involves CQAs upstream control of CQAS and reduced end product testing
- ❖ Justification for use of phosphoramidite starting materials – can prior knowledge of approval be used?