Use of Third Party Prior Knowledge and Platform Data

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22 October 2024

Outline

- Introduction and problem statement
- Guidance
- Generalized Examples/Scenarios
- Ways forward
- Acknowledgements

Introduction

- The concepts of platform data and prior knowledge are well established in the pharmaceutical industry
- Science and Risk based decisions also well established
- Science should be based on the broadest and most reliable data set possible
  - *Product knowledge*
  - *In house Knowledge*
  - *Scientific literature*
  - *Supplier knowledge*
  - *Collaborators…*

Introduction
New Modalities

- Oligonucleotides, Peptides, ADC's, Radio conjugates etc.
- Often use very similar (platform) technologies
  - *Manufacturing technologies; e.g. Solid phase synthesis, purification technologies etc.*
  - *Common raw materials; Nucleotide phosphoramidites, radio-isotopes, warheads and linkers etc.*
- Often have similar properties
  - *Stability*
  - *Impurity classes*
  - *Devices*

Introduction New Modalities

- Industry collaboration
  - Trade associations; EFPIA, EPOC, IQ Consortium etc.
  - Pre-competitive collaborations
  - Publications
    - Apparent impact of EPOC publications on draft EMA Oligonucleotides Guidance ☺

How do I use Platform Data That belongs to a different legal entity?

Guidance

- ICH
  - ICH Q8 Pharmaceutical Development

options and process parameters. This understanding can be gained by application of, for example, formal experimental designs*, process analytical technology (PAT)*, and/or prior knowledge. Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle[1] of the product. Such

An enhanced, quality by design approach to product development would additionally include the following elements:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including;
  - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs;

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of

Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. For an illustrative example,

Guidance

- ICH Q9 Quality Risk Management

3. PRINCIPLES OF QUALITY RISK MANAGEMENT

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)

- ICH Q10 Pharmaceutical Quality System

1.6.1 Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and *change management* activities.

- ICH Q11 Development and Manufacture of Drug Substances
  - "Prior Knowledge" mentioned 17 times
  - See later slides

Guidance

- EMA

Meeting Report:
Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications
23 November 2017, European Medicines Agency, London

https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party-quality-working-party-workshop-stakeholders-relation-prior-knowledge-and-its-use-regulatory-applications_en.pdf

- See later slides

Guidance

- EMA

Guideline on the Development and Manufacture of Oligonucleotides

Draft

Draft agreed by Quality Working Party	18 June 2024
Adopted by CHMP/PROM for release for consultation	15 July 2024
Adopted by CVMP for release for consultation	17 July 2024
Start of public consultation	22 July 2024
End of consultation (deadline for comments)	31 January 2025

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Guideline, oligonucleotides, solid phase synthesis, comparability, phosphoramidites, solid support resin, linker, conjugation, deprotection, coupling, capping, cleavage, pooling strategy, stereoisomers, deletion sequence, truncated sequence, insertion sequence, immunogenicity, sterilisation, generics, prior knowledge, active substance in solution, personalised medicines

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-development-manufacture-oligonucleotides_en.pdf

Guidance

- FDA

Platform Technology Designation Program for Drug Development
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

- Pathway for designation as a “platform technology” but does not preclude use of “prior knowledge”.

FDA acknowledges that the term “platform technology” has been used by both industry and FDA to describe technologies in ways that differ from the definitions of **platform technology**[4] and **designated platform technology** that are outlined in statute and this guidance. Some technologies that industry and FDA have historically considered to be platform technologies might not meet the statutory definition and statutory eligibility factors and, if not, would not be eligible for the designation program. Ineligibility for designation does not preclude a sponsor[5] from leveraging **prior knowledge** across applications.[6] FDA has allowed sponsors to leverage prior knowledge from previously submitted applications when authorizing or approving drugs in an application submitted by the same sponsor.

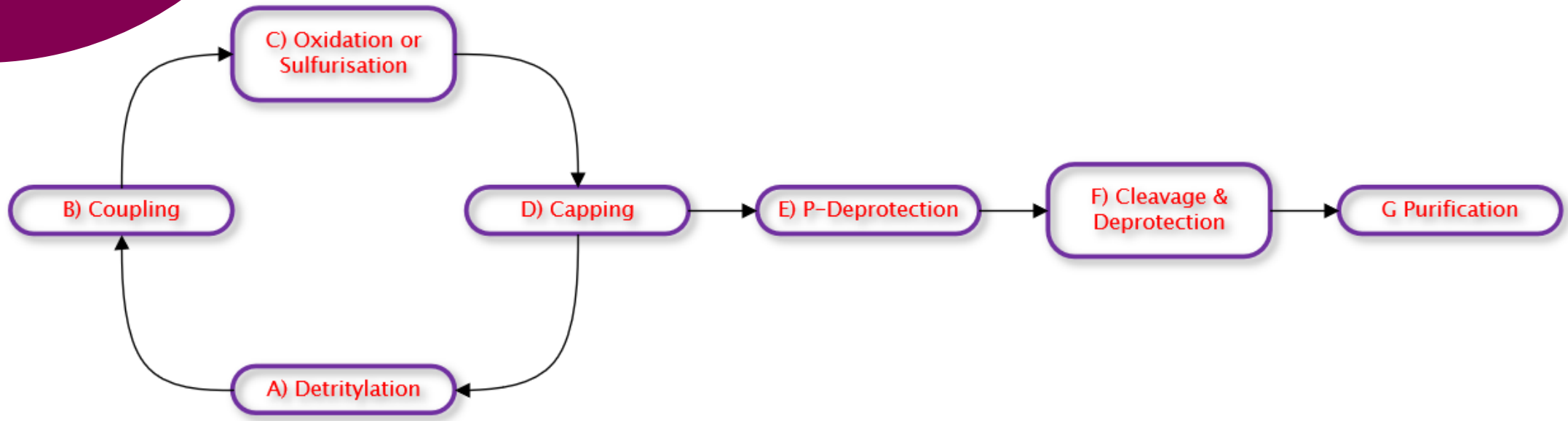
Guidance Conclusion

- The concepts of prior knowledge and platform data are well established
- Use of prior knowledge can facilitate development and registration of processes for the benefit of companies and patients
- Agencies encourage the use of prior knowledge and platform data
- Better science and risk-based decisions

- How do I use Platform Data That belongs to a different legal entity?

Examples
Oligonucleotide Manufacturing

- Solid Phase Synthesis
- Often a platform technology for a given company or CMO
- In house prior knowledge may be used to develop process, control strategy (CPP's and IPC's), analytical methods etc.



Examples
Oligonucleotide Manufacturing

- Oligonucleotide manufacture utilises different approaches to purification.
- Companies typically focus on one platform leveraging prior knowledge between products
- Cross industry approaches to impurity grouping (Capaldi et al.)
  - *Platform approaches within companies for both impurity management and analytical method development and validation*

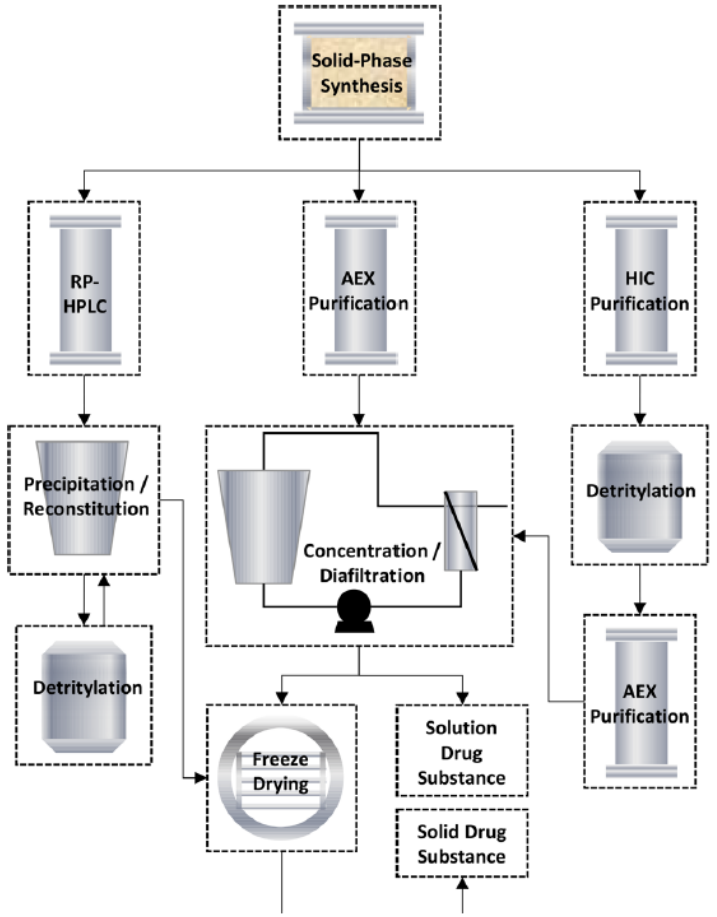
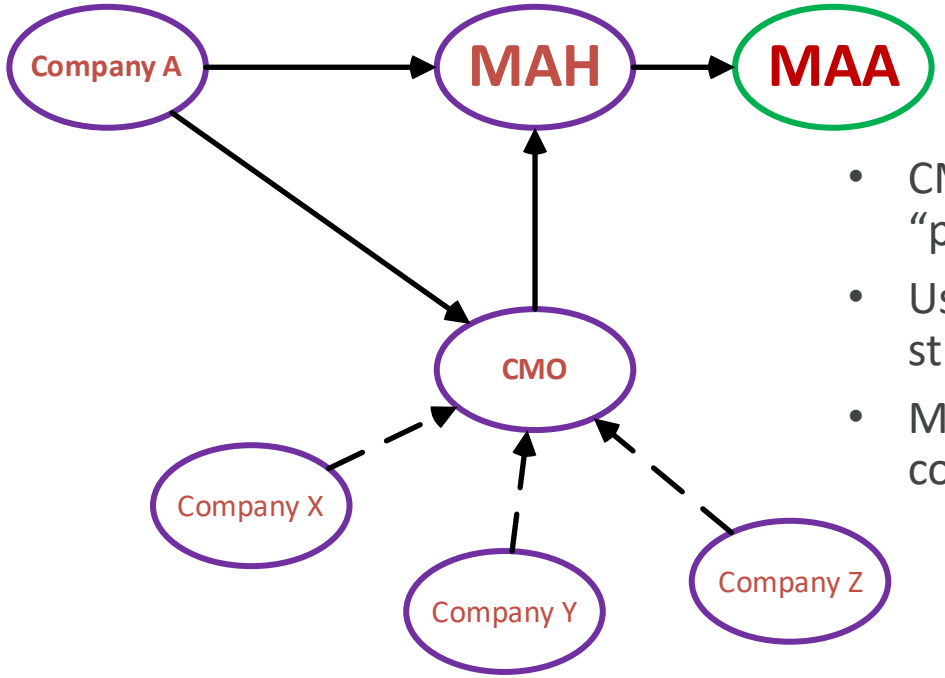


Figure 6. Generalized oligonucleotide solid-phase synthesis process highlighting three common postsynthetic pathways. Left: trityl-on RP-LC purification, solution-phase detritylation, precipitations, and freeze-drying. Middle: AEX purification with on-column detritylation, concentration/diafiltration, and freeze-drying. Right: HIC purification, solution-phase detritylation, AEX purification, and concentration/diafiltration.

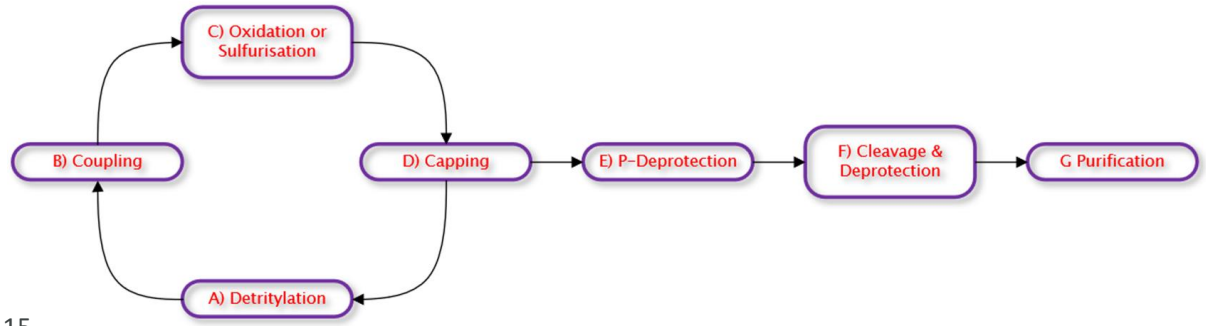
[14] Borths et al. OPRD 2023, 27, 1693–1702, Capaldi et al. Nucleic Acid Therapeutics, 2017, 27, 309-322

Examples
Oligonucleotide Manufacturing

- Company A licenses an asset to MAH
- Company A, the originator, may have a wealth of in-house proprietary knowledge
- Used to develop process, control strategy, analytical methods etc.



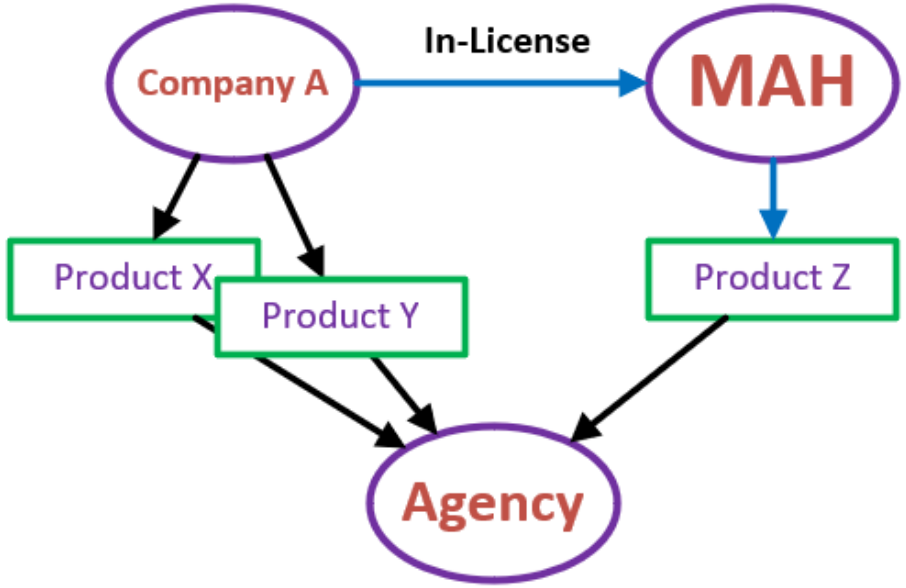
- CMO, may have a wealth of in-house "proprietary" knowledge
- Used to develop process, control strategy, analytical methods etc.
- May be subject to agreements with companies X, Y & Z however



What data can MAH use in their MAA?

Examples
Oligonucleotide Stability

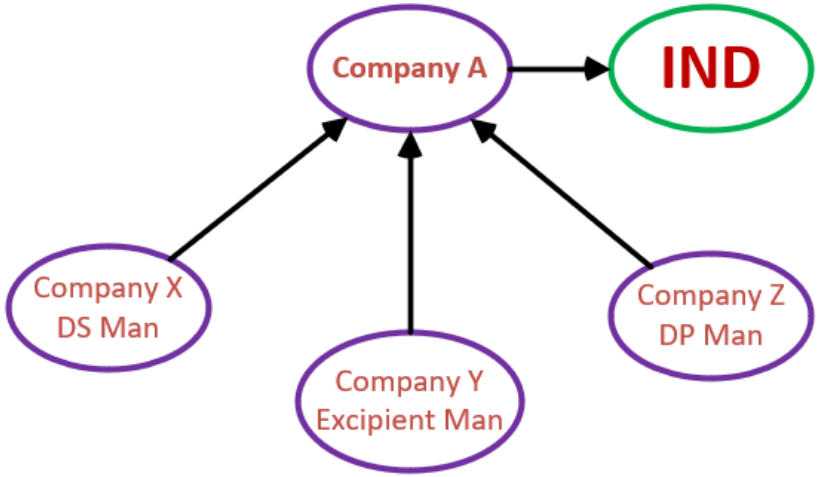
- Company A, the originator, may have extensive in-house proprietary knowledge
- The Agency may have seen a wealth of stability data from Company A's platform
  - Company A specialises in ASO's, mRNA, siRNA etc. so typical stability for a modality may be well understood
  - MAH only owns the data for Product Z however
  - For a late in-license, data may be limited with little time to gather more

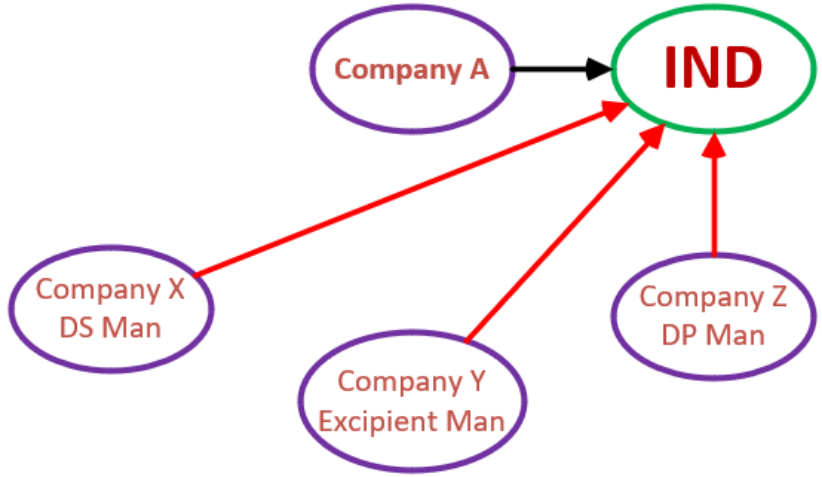


- Company A may own the rights (and MAA) for some markets and may have written the first dossier
- MAH may have to "convert" the dossier for other markets

Examples
Novel product technologies

- Company A, working with CRO/CMO's to develop a novel API/Excipient/DP
  - Companies X, Y and Z have specialist prior in-house knowledge
  - Companies X, Y and Z want to maintain some IP internally, i.e. not share all the details with Company A or each other
  - But agency won't accept parts of submission from more than one company
  - Can't do DMF/ASMF for excipient





Ways forward
ICH Q11

Page 2

experience. Data derived from relevant prior knowledge, including platform manufacturing (see Glossary) can be leveraged to support development of the commercial process and expedite scientific understanding.

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3.2 Submission of Manufacturing Process Development Information

The information provided on the development of the drug substance manufacturing process (primarily in Section 3.2.S.2.6 of the application) should identify significant changes during process development, link relevant drug substance batches with the developmental stage of the manufacturing process used to prepare them, and explain how prior knowledge, risk assessments, and other studies (e.g., experimental, modelling, simulations) were used to establish important aspects of the manufacturing process and control strategy. Process development information should be logically organised and

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evaluated during development of a design space. Where development refers to specific prior knowledge, the relevant information and data should be provided and, where appropriate, the relevance to the particular drug substance should be justified.

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10.3 Example 3: Presentation of a Design Space for a Biotechnological Drug Substance Unit Operation

This example is based on a design space for a drug substance purification unit operation (Q-anion exchange column run for a monoclonal antibody in flow-through mode), determined from the common region of successful operating ranges for multiple CQAs. This figure illustrates a potential depiction of a design space based on successful operating ranges for three CQAs and the use of prior knowledge (platform manufacturing) in developing a design space. The ranges represented here indicate areas of successful operation. Operation beyond these ranges does not necessarily mean that drug substance of unacceptable quality will be produced, simply that these operating conditions have not been studied and therefore the quality of the drug substance is unknown.

Ways forward
FDA

Designation of a platform technology does not give third parties additional rights to reference information from an approved product application containing that platform technology if they do not own or have full rights of reference to it. In addition, a BLA holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license.[8] Any referencing of data or information by an application based on a platform technology designation should be consistent with this general expectation. Any relevant information regarding a full right of reference agreement should be submitted with the administrative documents that are included in Module 1 of Electronic Common Technical Document (eCTD) submissions.[9]

A different sponsor may also be able to leverage platform technology data if they receive a full right of reference to the leveraged data under a business arrangement with the originator of the platform technology.[15]

FDA Platform technology designation guidance discusses “full right of reference” to allow cross referral.

Ways forward
Agency View

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It was noted that publication of 'generalisable' internal knowledge could be a way to increase transparency and scientifically validate the evolving knowledge to foster new or changes to existing guidelines.

Page 2

It was generally agreed that, in the context of pharmaceutical development and regulatory applications, prior knowledge source can be **internal knowledge** from a company's proprietary development and manufacturing experience (e.g. historical experience based on similar compounds, products and processes, application of 'platform technologies', knowledge from previous filing) or **external knowledge** such as reference to scientific and technical publications (including literature and peer-reviewed publications) which can be used to inform the application of established scientific principles (e.g. chemistry, physics and engineering principles, mechanistic understanding from studies evaluating structure-function relationships). It was noted that publication of 'generisable' internal knowledge could be a way to increase transparency and scientifically validate the knowledge.

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Several questions arose with regards to the level of detail that is needed to capture prior knowledge in regulatory dossiers, as well as how it could be best presented and maintained in a dynamic way so that it can be reusable across products without unduly expanding the volume of regulatory dossiers. The evolution / transition of prior knowledge from questioned to generally-accepted prior knowledge is important.

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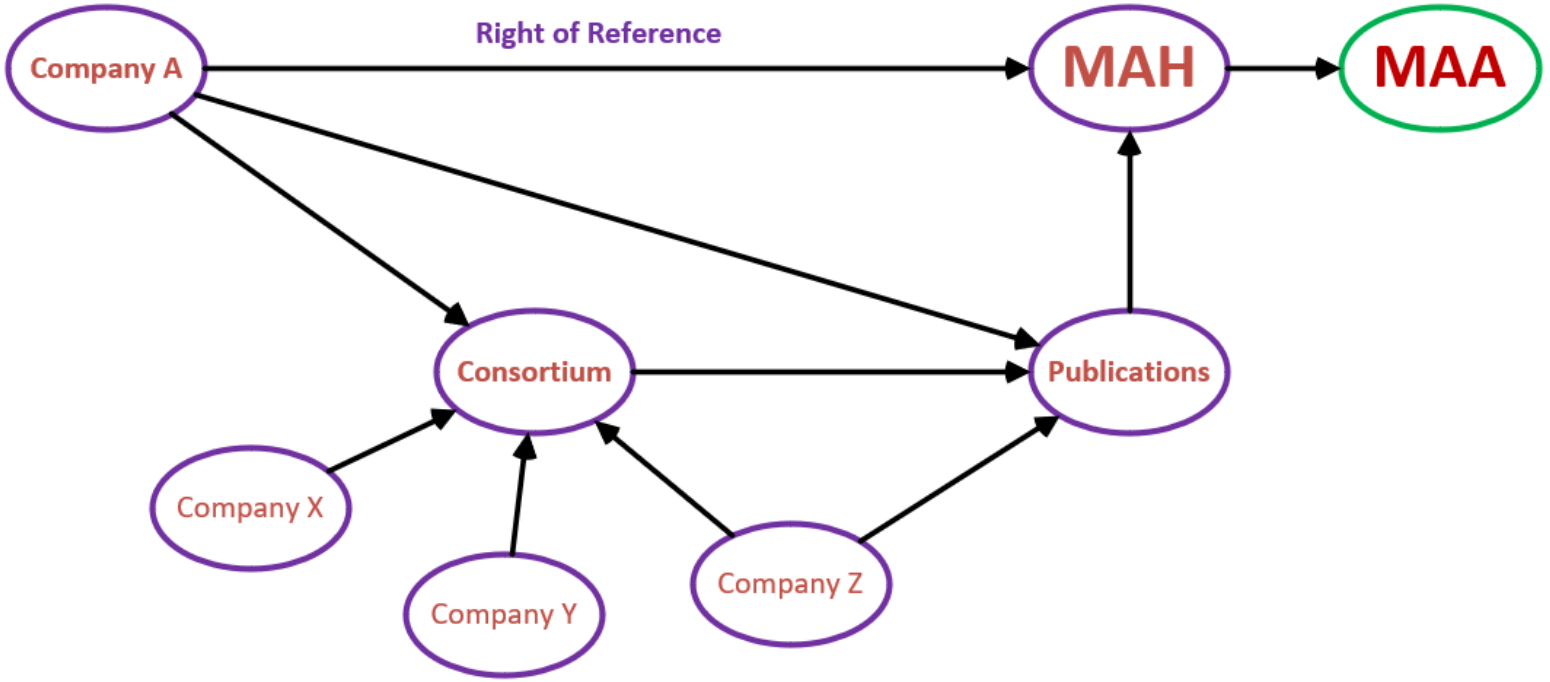
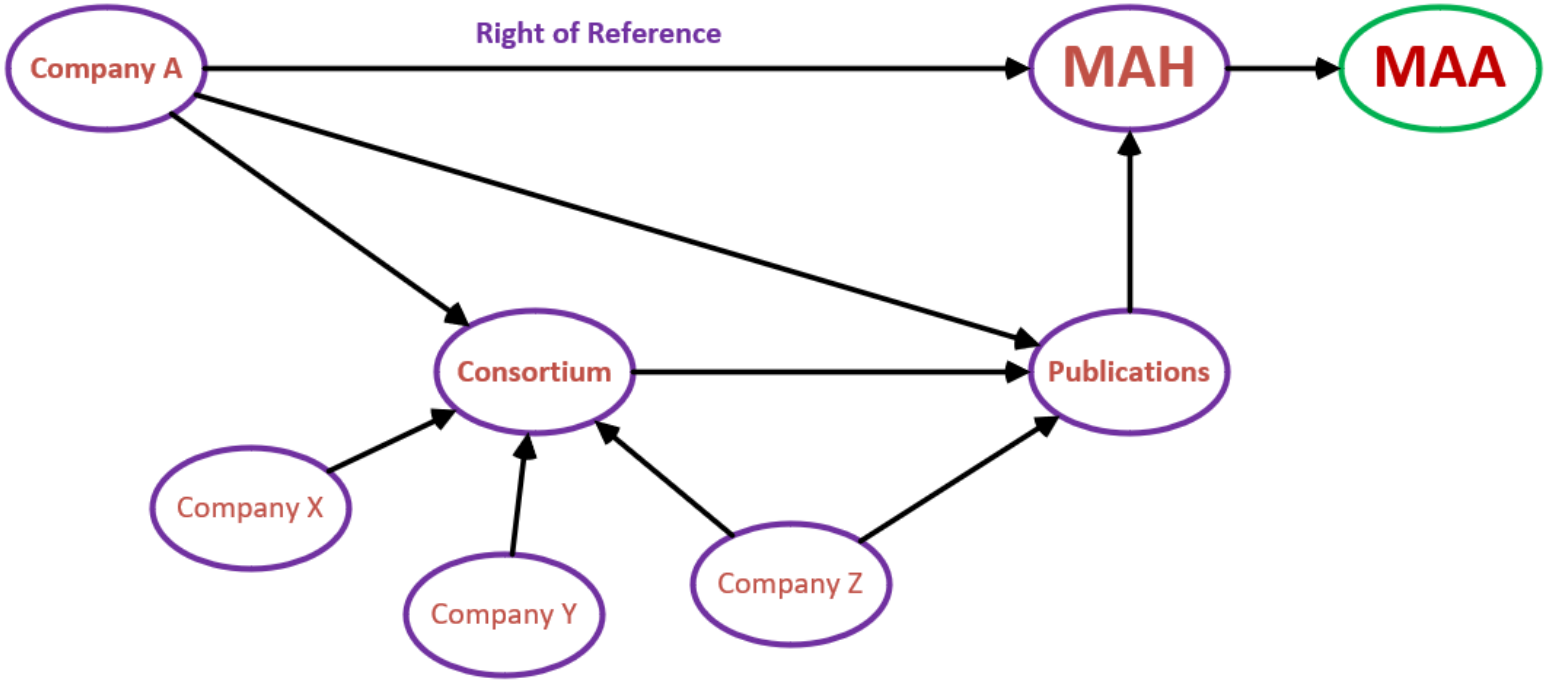
Ways forward Industry



- Company A shares Right of Reference with MAH
- Company A publishes platform data
- Company Z publishes platform data
- Company A shares data with companies X, Y and Z through pre-competitive consortium
  - Consortium publishes
- Other scenarios?

Ways forward Industry



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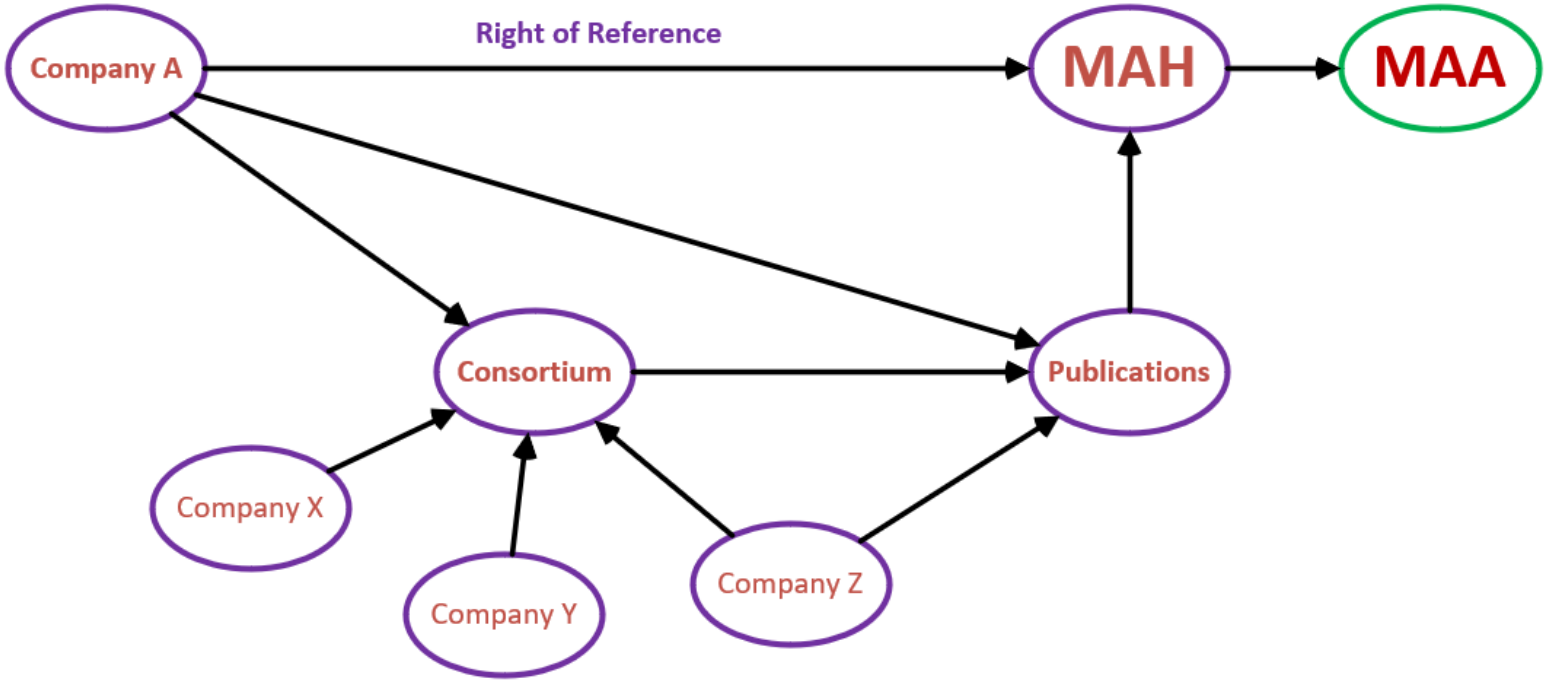
Ways forward Discuss



- What experiences do others have?
- What platform data would be useful to publish (Stability?)
- How does prior knowledge become generally-accepted?
- How else could we address this?

Acknowledgements

- Organising committee
- Jenny Franklin and Tracey Burr (IONIS)
- Karin Grosch and Kate Arnot (AstraZeneca)
- Speakers and Panellists