

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

Introduction - General considerations from industry

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Outline

1. What is it?/ Definition
2. What of such knowledge is applicable for my specific case?
3. How can such knowledge leverage my (specific) development?
4. How to convince others that this is justified?/
How to present it?
5. What to expect today?

What is it?



1. What is it?/ Definition

- Brainstorming in the OC:
 - *Knowledge you have from relevant own experience/ textbooks/ scientific papers etc.?*
 - *Any knowledge that is not specifically product-related (in the public domain or internally documented)?*
- «Google»: *Total knowledge of an individual (and/ or a company?) as of now?*
- Challenges:
 - **Where to draw the line?** Examples: significance of C-terminal Lysine, sterilization done at 121°C → no need to revisit, part of the «regulatory/ established system»;
 - However, it is a **moving target**: there is an evolution, a «prior knowledge life cycle»
 - **Proprietary knowledge/ previous products** - being «close enough» («similar») to former products → Process of showing similarity could be laborious (see biosimilars)

1. Definition cont'd/ ICH and prior knowledge (1/2)

- ICH Q8(R2): mentions “prior knowledge” several times, esp. in examples
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107636.pdf

➤ “Knowledge management (as described in ICH Q10) can also facilitate manufacturing process development. In this context, potential sources of information can include **prior knowledge** and development studies. **Prior knowledge can include established biological, chemical and engineering principles and applied manufacturing 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.”

1. Definition cont'd/ ICH and prior knowledge (2/2)

- **ICH Q10: mentioned under *knowledge management***
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

➤ “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.”

1. Definition/ Some more thoughts on «what is it?»

- **Internal knowledge from development and manufacturing:**
 - Historical experience based on similar compounds, products and processes
 - Includes information that results from modelling of historical information
 - Application of ‘platform technologies’ (see slide 13)
 - Knowledge from previous filings (proprietary medicines)
- **External knowledge:**
 - Reference to scientific and technical publications (including literature and peer-reviewed publications)
 - Vendor’s data etc.
- **Application of established scientific principles:**
 - Chemistry, physics and engineering principles
 - Mechanistic understanding, e.g. studies evaluating structure-function relationships
 - *Question again (cf. slide 4): Where to draw the line?*

2. What of such knowledge is applicable for my specific case?

and

3. How can such knowledge leverage my (specific) development?

- Will be discussed in the general considerations and case studies of the different sessions following this introduction

2./ 3. – some «teasers» extracted from case studies (1/2)

Product Design

- **Prior knowledge (platform technology) often applied to monoclonal antibody (MAb) products** to improve speed and robustness, allows front-loading of certain activities (assessment of **CQAs, CPPs**)
- Candidate molecule fit with platform **may not guarantee success** – small differences in molecular structure could lead to large difference in behavior for biotherapeutic products
- Increasing interest in **Product-class Monographs**, they could be an opportunity:
 - to inform list of typical Quality Attributes and information on specific class of product from which key part of testing strategy can be derived, also to differentiate between characterization and release/stability testing
 - may be challenging for complex biological products which possess large number of quality attributes.

Process Development

- Prior knowledge is widespread in small and large molecules development, for drug substance & drug product
- **Less experimentation to support process development may be appropriate when working in well-understood and well-precedented areas**
- Prior knowledge can be leveraged together with small scale manufacturing experience to optimise approaches to validation and post-approval changes.

2./ 3. – some «teasers» extracted from case studies (2/2)

Control Strategy

- Currently, reporting of Prior Knowledge is **mostly limited in assigning criticality**
- **Short/medium term future:**
 - More upstream translation of testing from specification to process
 - Reduced testing of certain ‘historical’ CQAs (e.g. residual DNA, HCP)
- **Long-term future:** through experience, more attributes generally accepted as safe, driven by Prior Knowledge evidence.

Accelerated pathways

- Identify/ create opportunities to **agree early in accelerated development on how companies can leverage prior knowledge**
- Discuss mechanisms for “**smaller, more rapid**” decisions (eg. protocols, “living” DMF, rolling submission)
- **Ensure flexible approach/ options to how prior knowledge could be presented in a submission:** based on prior knowledge package and product data to be presented.

4. How to convince others that this is justified?/ How to present it?

Problem Statement

- Current lack of understanding on how to present and maintain prior knowledge (PK) in regulatory submissions (CTD format has limitations)
- MAHs need to **reproduce the same or similar information** in regulatory dossiers (information which has often already been assessed/approved by a competent authority)
- To make more effective use of prior knowledge, **good understanding among regulators and industry on how it should be presented/ documented in regulatory dossiers is essential**
- Particularly important in the EU where 'stand-alone' dossiers are required thus limiting use/ value of cross-references
- Use of PK in context of post-approval variations needs to be considered as well; limited procedural flexibility to use worksharing across multiple products.

4. How to convince others that this is justified?/ How to present it?

Submitting exactly the same information

- For example, excipients, analytical methods, device and other potential common parts of the dossier, as for a previous submission
 - Use of a '**Master File**' (DMF-type approach) for this type of information could be considered, where the relevant information can be reviewed and approved once by a competent authority and then cross-referenced in subsequent submissions
 - As the information needs to be kept current, use of a DMF would also facilitate lifecycle management through ongoing data maintenance and exchange with regulators
- *Alternatively, are there other already existing mechanisms or ideas for new tools to solve the issue?*

5. What to expect today?

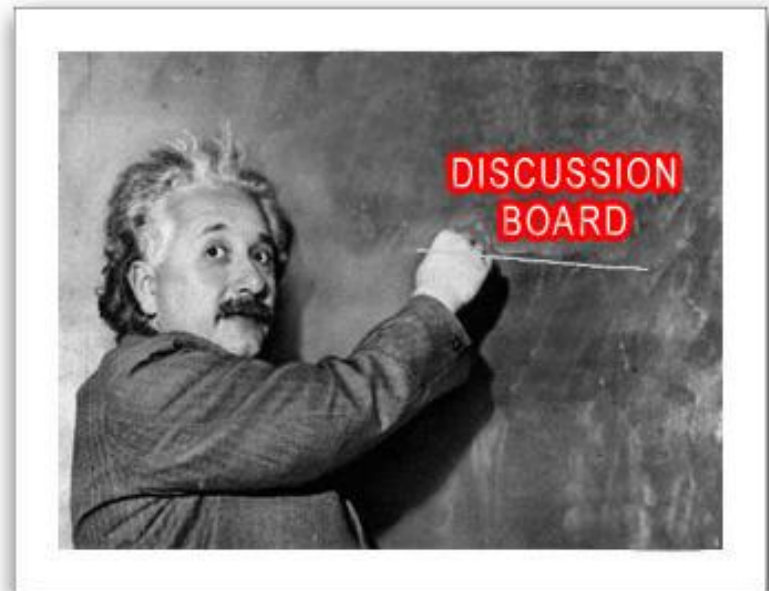
- Important: what is Prior Knowledge (PK) concretely used for in the end?
 - All subsequent sessions will address this point
- We will present a number of examples showing what is PK...
 - ... And thereby also clarifying what we think is not PK.

And one last «polite request»

Please participate actively in the discussions

...and enjoy the day!

THANK YOU--



Backups

4. How to convince others that this is justified?/ How to present it?

- Concrete example, see discussion of a **master file concept** for viral clearance data in: <https://www.ebe-biopharma.eu/wp-content/uploads/2017/04/ebe-platform-manufacturing-concept-paper-1-mar-2012.pdf> (pp. 17-20)
- Currently, master file system does not exist in EU for biologics, except **Plasma Master File (PMF)/ Vaccine Antigen Master File (VAMF)**

european biopharmaceutical enterprises

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**Platform Manufacturing of Biopharmaceuticals:
Putting Accumulated Data and Experience to
Work**

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6.	Presentation of Platform Process Data for Regulatory Review
7.	Conclusions

➤ **Biologics/ Drug Master Files, if instituted in the EU, would add value.**
Scope could include DS, DP, raw materials, diluents, novel excipients as done in the US/other regions with the DMF/ BMF system.

4. Some points to consider regarding the Vaccine Antigen Master File (VAMF)

- A VAMF is a stand-alone part of the MA dossier related to one specific vaccine antigen which is common to several vaccines from the same MA applicant or MAH (EMEA/CPMP/4548/03 March 2003)
- VAMFs are limited to antigen drug substances

Use of VAMFs is rare/ non existing - reasons:

- Complexity in life cycle setting (changes require certification at antigen *and* drug product level) $\leftrightarrow$ other procedures such as worksharing provide more flexibility
- *VAMF is applicant specific* $\leftrightarrow$ different from BMF/DMFs where multiple applicants can x-refer
- During the VAMF certification procedure $\rightarrow$ *black out period for variations*
- *VAMFs out of scope for influenza vaccines*
- VAMF certification *prior* to the submission of MAA $\leftrightarrow$ BMF/DMFs already under IND.