Using prior knowledge in applications

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Establishment of the product design and manufacturing process ➡ Product Quality

- **Neither the product design nor the manufacturing process have to be optimized to result in the absolutely highest purity, longest shelf life etc achievable.**
- **The manufacturing process should reproducibly deliver a product of an appropriate quality to assure its safety and efficacy as determined in clinical trials over the complete shelf life .**

Prior knowledge

- **“No problem can be solved from the same level of consciousness that created it.”** *Albert Einstein*
- **Indispensable tool for taking the right decisions early on- learn from history - and is therefore, directly or indirectly and on purpose or not, always included in planning for new products/ manufacturing changes etc.**
- **May lessen the burden for product specific data at certain stages.**

Use of prior knowledge already identified in EU guidelines

Examples from the EU BWP + QWP PV guidelines

Drug substance (BWP)

- ***Process development***
  - Documented **prior knowledge** and risk assessment are valuable tools to identify and justify the material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters which have the potential to affect the active substance critical quality attributes (CQAs) and/or process performance.
- ***Process evaluation***
  - **Prior knowledge** (for example platform data) can be used as supportive information. The contribution of these data (e.g. to justify operating ranges, input set points) to the overall validation package will depend upon justification that the data is representative of the proposed commercial process.

Drug Product (QWP+BWP)

Continuous process verification

- Sufficient knowledge and understanding of the process is required in order to support continuous process verification. However, the scope and extent of continuous process verification will be influenced by a number of factors including:
  - **prior development and manufacturing knowledge** from similar products and/or processes;
  - the extent of process understanding gained from development studies and commercial manufacturing experience;
  - …

Use of prior knowledge already identified in global guidelines

- **Q8(R2), Q10**
- **ICH Q-IWG training workshop 2010**
  - Prior knowledge may include
    - Internal knowledge from development and manufacturing
    - External knowledge: Scientific and technical publications (including literature and peer reviewed publications)
  - Citation in filing: Regulatory filings, internal company report or notebook, literature reference
  - No citation necessary if well known and accepted by scientific community

Use of prior knowledge already identified in global guidelines

- **ICH Q-IWG Points to consider (2011)** addresses prior knowledge in several aspects:
  - In consideration for identifying and documenting CQAs and CPPs
  - In applying a risk based approach to the assessment of suitability of control strategy across different scales
  - In determining factors for studies in DoE´s and selection of variables for models
  - In the case of well-established first principles-driven models, prior knowledge can be leveraged to support model validation and verification, if applicable
  - If used should be part of the documentation to support QRM decisions, models, design space etc.

Common issues arising

- **Definition: Where to draw the line between what is common (textbook) knowledge and what is (proprietary) prior knowledge?**
  - Main topic of this workshop will be the latter category
- **What needs to be documented in the file?**
  - Clarity of expectations is key
- **In which form?**
- **Where?**
  - Preferably where the product specific documentation it replaces would be placed

Risk based approach to level of detail in process development

- **Prior knowledge is always taken into account when establishing new processes or improving already existing. What to document in the file?**
  - **Development** of a rough process description can to a great extent be built on prior knowledge. Less need for detailed descriptions of these studies.
  - **Evaluation** studies in small scale to set the outer boundaries of the process ranges need to be described in more detail. Normally data from the actual product is expected. In case reference is made to prior knowledge, these studies should be described and the applicability for the given process needs to be justified.
  - **Verification** studies- Normally expected to be performed with actual product. Use of protocols/ fewer batches will depend on the relevance of the data to predict the outcome.

Extrapolation process

- **Proof of validity of extrapolation is key for acceptance of prior knowledge.**
  - Within a platform (e.g. Mab, synthetic peptides/ oligonucleotides)
    - Should be possible but would still need justification. (i.e. is all parts of the process run in the same manner (load, conditions etc)
  - Between different products (e.g. Mab vs EPO)
    - More difficult but possible for certain principal features.
    - May be OK for process development but likely to need evaluation data.

Extrapolation attribute criticality

- **Risk based assessment**
- **Will depend on type of product, indication, posology**
- **Certain established dogmas**
  - C-terminal lysines
  - DNA
- **Case by case assessment**
  - Product related substances/ impurities (acidic/ basic species, glycoforms etc.)

Prior knowledge applied for Accelerated scheme products

- **Process validation will be a rate limiting step. To what extent is it possible to rely on prior knowledge/ small scale studies to base approval?**
- **Extrapolation to be justified**
  - Processes are rarely absolutely identical, neither are physico-chemical properties of molecules.
  - Indication + dosage to be considered
- **Expected that a broader batch wise control is established for e.g. breakthrough therapies until more product specific experience is gained**
- **Protocols/ On-going (continued) process verification**
  - These would be based on small scale data from actual product and prior knowledge from upscaling, transfer etc of similar products

Master files as part of Prior knowledge in an application?

- **is using an ASMF for a chemical active substance a type of prior knowledge?**
- **is using a CEP for an active substance a type of prior knowledge?**
- **is using a PMF a type of prior knowledge?**
- **The use of master files will avoid redundant reassessment of the same documentation.**
- **The master file concept as such will not support the design of products, processes and control strategy, i.e. the main topics of this meeting.**
  - Prior knowledge from a contract manufacturer may be used in designing products/ processes/ control strategy if justified.
- **Extended use of master files systems (excipients/ packaging material etc.) is not possible within current legislation.**
  - Even if identicial to earlier submissions, currently the same information on excipients, packaging material etc. need to be submitted with a new MAA. Clear references to in which products the material already was submitted and assessed and a justification of the relevance for this assessment for the new MAA will minimize the need for redundant reassessments.

Thank you