Summary of EMA Workshop on prior knowledge and its use in regulatory applications

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Some meeting facts

• Meeting took place at EMA in London on November 23, 2017
• Participants:
  - 51 regulators & 49 industry representatives
• Both small molecules and biologicals
• Meeting was live-broadcasted (> 300 participants)
• All information (agenda, presentations, meeting report) can be found under this [link](#)
Agenda

1. What is Prior Knowledge?
2. Using prior knowledge in product development/design?
3. Using prior knowledge in process development & manufacturing strategy?
4. How to use prior knowledge in defining the control strategy?
5. Experiences of accelerated access approaches (i.e. PRIME)
6. General discussion, summing up and way forward
Questions to be considered:

- What is (and isn’t) considered to be prior knowledge?
- How can such prior knowledge be used in regulatory submissions?
- How to justify its use?
- How to present it in the dossier?
What is prior knowledge?

- As such nothing new. Mentioned in ICH Q8, Q10 and EMA Guidelines.
- **Internal knowledge**: from development and manufacturing
- **External knowledge**: Scientific and technical publications (including literature and peer reviewed publications)
- Application of established scientific principles
- What is **common (textbook)** knowledge and what is (**proprietary**) prior knowledge?
- Receiving SA from an agency should also be considered as prior knowledge (agencies have overview of all products in clinics/ on the market)
- Benefit of prior knowledge in **lifecycle management** – risk assessments, variation classification, post authorisation tools (e.g. PACMP)?
What is prior knowledge?

• Developers and assessors need to share a consistent, scientific understanding of the available prior knowledge and level of understanding in order to facilitate the development of products and the full implementation of ICH Q8-12.

• The extrapolation and justification of applicability of prior knowledge is key, e.g. within a product class and between product classes. The company’s (applicant’s) experience and manufacturing site experience is key to the risk assessment. Underpinning, full data should be available to assessors to support the prior knowledge justification.
  ➢ Justification is key. The decisions are based on totality of data.
What is prior knowledge?

- The **evolution / transition** of prior knowledge from questioned to generally accepted prior knowledge is also important
  - e.g. can evolving prior knowledge result in the establishment of new or changes to existing scientific guidelines
- **Transparency, qualification** of prior knowledge, **publication** all increase the chance of it to be accepted
- CQA assignment based on Prior knowledge needs to take indication and posology into account
- Prior knowledge can be used to **inform risk assessments**
  - defining **CQAs, CPPs, IPCs, PARs**, small scale studies, full scale **validation** plan
  - linking to quality **risk to safety and efficacy.**
What is prior knowledge?

- **Avoiding reassessment** of duplicate data is an aim
  - Master file concept suggested by industry
  - Regulators focus is on the demonstration of **applicability of the knowledge to the current product**
    - e.g. via clear cross-reference and/or provision of detailed information in the dossier
    - Master files for biologicals, excipients, packaging are currently not possible in EU dossiers
- ‘**We are not opening the door to prior knowledge. The door has been already open for some time.**’
How to present it in the dossier?

General comments

• **Where & what in the dossier?** Simple cross-reference to other product, basic summary statistics, **graphical summary**, full tabular version of prior knowledge
  - Info relevant to the assessment of the MAA should be presented in the dossier – in line with Directive 2001/83/EC as amended
• The intended purpose for including the prior knowledge should be made very clear. i.e. **what does it replace?** This will determine the appropriate sections of the dossier where the documentation should be placed
• In case of doubts - ask for scientific advice from EMA or MS (national SA)
• **Prior knowledge** could be present in:
  - Scientific Advice letters, pre-submission meeting minutes (if appropriately flagged for assessor)
  - Supportive dossier sections: 3.2.S.2.6, 3.2.P.2, 3.2.A, 3.2.R
Product development/ design

- Prior knowledge of **active substance**, **excipient** or **packaging** properties from similar products to support formulation design;
- **platform knowledge**; platform technologies, platform design space
- identifying **CQAs**, informing **risk assessments**
- predicting **stability and issues with scale up**
- **Product class monographs** v Product specific monographs?
- **extractables / leachables**
- physiology based **modelling**, e.g. Gastroplus
- **Expanding** the use of **prior knowledge** across multiple types of products. How to apply prior knowledge from **similar products or different product classes** to a product in development?
Product development/ design

- Case Study 1: FIM to commercial for a lyophilised (NBE) product
- Case Study 2: Development of a lower dose paediatric strength IR tablet
- Case Study 3: Use of platform technologies for Adenovirus-based vaccines

- Prior knowledge informing risk assessments – CQAs linked to QTPP
- Applicability / qualification of a platform to a new molecule e.g. ‘mAbs’; ‘family products’
- Core CQAs/CPPs for a ‘family product’ platform approach
- Need to adapt a product’s development (‘trade-off’) so prior knowledge remains relevant.
If molecules exhibit comparable characteristics (e.g., stability profile) and standardized process are applied for drug product manufacturing, the respective Design Spaces will overlap.

Within the overlap, a smaller *Platform Design & Control Space* can be defined applicable for all following “next-in-class molecules”.

**Conventional Approach to define Design & Control for X-mAb**

- Control Space
- Design Space
- Knowledge Space

**Platform Design & Control Space for multiple next-in-class mAbs**

- Platform Control Space
- Platform Design Space
- x, y, z mAb Design Spaces
- Knowledge Space

**Diagram Illustration**

- X-mAb
- z-mAb
- y-mAb
Product development/ design

• Presenting the **info in the dossier**?
  - Extent will depend on the intention of the study (support early development vs late changes)
  - Reproducing full / part information
  - Cross reference to previous assessments
• For **lifecycle management** - use of broad protocols?
• Prior knowledge in the **establishment of public standard**
• EDQM working on developing general monographs and product specific monographs
  - e.g. Infliximab Ph Eur
Process development & manufacturing strategy

- Sources of knowledge; scientific literature, common industry product & platform knowledge, specific company product & platform experience
- Synthetic process design, predicting drug substance physical properties, platform formulations (i.e. dosage forms, excipients, manufacturing process).
- Scale up and validation, lifecycle management (e.g. analytical methods, PACMP).
  - e.g. BCS classification, process modelling, packaging, stability
How might prior knowledge look in the dossier for defining CPPs?

Seán Barry, HPRA, IRL

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CPP = Critical process parameter
KPP = Key process parameter

Prior knowledge

Combination of prior knowledge and product-specific data presented in the dossier

Product specific
Process development & manufacturing strategy

- Case Study 1: Application of prior knowledge to process parameter definition
- Case Study 2: Validation Efficiencies from QbD & Prior Knowledge

- Setting acceptable ranges for CQAs, informing risk assessments: linking PP+CQAs,
- “Prior knowledge assessments” (e.g. platform mAb chromatography purification step) linking to control strategy. Depending on the impact the level of prior knowledge (and product specific data) needed to support a claim will differ. The more products in the platform, the higher the chance of acceptance.
- Use prior knowledge to reduce uncertainty in risk assessments.
- Commonality across multiple products (e.g. mAbs)
- Use of prior knowledge to classify certain process parameters as non CPP for next products; industry and regulators to focus on those parameters which are relevant for product quality.
Process development & manufacturing strategy

• Using **computational models** and **leveraging automation**, batch record review. Together with acceptable established acceptance criteria for column performance monitored in each run may make the need for small scale data to support column re-use redundant.

• Certain processes (e.g. aseptic filling, leachables/extractables) for which extensive prior knowledge is available may be **justified as ‘standard’ manufacturing technology**.
Establishment and application of Column Reuse Model - Frank Zettl, Roche (case study 2)

1) Model is generated using small scale data from Mab A

2) Model is trained and extended on small scale MAB A data and large scale Mab B data to predict impact of reuse cycles
   -> Patterns across datasets are predictive for impact of reuse cycles on yield

3) To avoid overfitting while making best use of all available data a cross validation approach is used

4) The models are capable to replace the currently used small scale re-use studies
   - monitoring of predictive patterns
   - continuously improvement with new data from manufacturing
Process development & manufacturing strategy

• **Case Study 3: Prior knowledge to streamline viral safety and resin lifetime studies**

• **Parvovirus only at nanofiltration;** could be acceptable for biotech products and established filters, note that experience has been gained in CTAs and some MAAs. The interpretation of ICH Q5A is important.

• **Virus filters alt low pressure/pressure release:** low pressure is considered critical. More knowledge from parvovirus retention under worst case conditions is desired.

• **Proposals for aged Protein A resins;** could be acceptable if prior knowledge has been published in scientific journals and/or in the viral clearance meeting reports.

• Where in dossier? The section **where it is used** (3.2.A (appendix) in this case)

• Potential next steps: meeting report; further discussion by BWP.
EBE suggestion: “viral clearance master file” (source see: link)
Control strategy

• Problems arising from tight specifications: batch rejections, less flexibility for shelf-life extensions, site transfers & process changes… delayed patient access?
• **Identifying CQAs**, clinical safety thresholds
• Risk-based specification setting:
• **Clinical exposure + appropriate prior knowledge** *(i.e. platform clinical and non-clinical experience)* = justified specifications?
  - Possibly an acceptable approach if scientifically justified but:
    - CQA assignment + limits based on Prior knowledge need to take **indication and posology** into account
    - Product **consistency** versus **safety and efficacy** is key
    - How will company **manage in the PQS**?
  - **Prior knowledge broadens** understanding of product specific data
Control strategy

• Case Study 1: Specification Setting for a Multivalent Vaccine
• Case Study 2: Oligonucleotide Control Strategy
• Case Study 3: Prior Knowledge in the Control Strategy for Biotechnology Products
• Case Study 4: Prior Knowledge for Setting Acceptance Criteria

• Oligonucleotides as a “Family product” – need for guidance / standards?
• Use for severity scoring in risk assessments. Criticality of QAs
• Prior knowledge from clinical exposure and in vitro / animal data?
• Statistical approaches to specification setting for lifecycle management.
• Experience from clinical exposure (e.g. reference products)
Accelerated access approaches (i.e. PRIME)

- Case Study 1: Avelumab: integrated Mab example
- Case Study 2: Atezolizumab: a case study of accelerated development

Prior knowledge can support flexibility in data compilation/delivery during accelerated assessment

Prior knowledge should:
- Be made available for assessment in order to facilitate a consistent review across regulators
- Its relevance and justification for use should be agreed with Regulators early (i.e. SA) for better plannability
- Its way of documentation should be agreed
- Dynamic and evolving amount of data should be made available over regulatory submission (incl. regulatory tools → recommendations, PACMPs)

Acceptability of prior knowledge to support quality package & conclusions → matter of assessment (case-by-case approach)
Regulatory expectations accelerated procedures – Veronika Jekerle, EMA

Regulator’s expectations

- Prior knowledge accumulated & documented
- Relevance of Prior knowledge determined
- Prior knowledge included into CTD (Module 3)
- Prior knowledge assessed
- Prior knowledge used to support life-cycle

Applicant & Regulators
- Kick-off meeting
- Scientific advice
- Pre-submission

Applicant
- SA letters
- Minutes Module 3
- (3.2.S.2.6. vs. 3.2.S, 3.2.P 3.2.A/R)

Regulators
- Assessment of Relevance/acceptability
- Impact on benefit-risk
- Recommendations/Annex II

Applicant & Regulators
- Planning of lifecycle
- PACMP
- Variations
- Line extensions

MAA approval
Challenges…

• Fear of sharing too much information (i.e. Prior Knowledge). Assessors going back to previous assessments etc. …
• Advanced planning for use of prior knowledge under accelerated conditions (and agreement with regulators)
• Recurring topic: deferral vs. removal of studies to be performed for regulatory submission(s) based on prior knowledge – can also turn out to be big opportunity for the whole concept, if properly presented & justified
Conclusion

- Prior knowledge has always been used in development of new products but not always clearly been spelled out. How to make further use of it?
- The extrapolation and justification of applicability of prior knowledge is key, e.g. within a product class and between product classes. The company (applicant) experience and manufacturing site experience is key to the risk assessment.
- Developers and assessors need to share a consistent, scientific understanding of the available prior knowledge and level of understanding in order to facilitate the development of products and the full implementation of ICH Q8-12.
- Transparency, qualification of prior knowledge, publication all increase the chance of it to be accepted.
- Prior knowledge has been successfully applied in vaccine applications over the years.
Next Steps

• Publication of video recording of the workshop on EMA website

• Follow-up discussions; BWP/QWP, interested parties, consider further guidance (e.g. Q&As)?
# Acknowledgements (entire WS organizing committee)

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Thank you.