EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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6. General discussion, summing up and way forward

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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?

Session 1 – what is prior knowledge?

- 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?
- The **evolution / transition** of prior knowledge from questioned to generally accepted prior knowledge is important
  - e.g. Can evolving prior knowledge result in the establishment of new or **changes to existing scientific guidelines..**

Session 1 – what is prior knowledge?

- The **extrapolation and justification of applicability** of prior knowledge is key, e.g. within a product class and between product classes. CQA assignment based on Prior knowledge need to take indication and posology into account
- Prior knowledge can be used to **inform risk assessments**
- **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.

Session 2 - 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**
- **Product class monographs** v Product specific monographs?
- **extractables / leachables**
- physiology based **modelling**, e.g. Gastroplus
- how to apply prior knowledge from **similar products or different product classes** to a product in development?

Session 2 - 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.

Session 2 - product development/design

Predicting issues with **scale up.**

Presenting the **info in the dossier ?**

- 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?

Addressing prior knowledge in **Scientific Advice** procedures

Prior knowledge in the **establishment of public standard**

EDQM working on developing general monographs and product specific monographs

e.g. Infliximab Ph Eur

Session 3 - process development & manufacturing strategy

- Using prior knowledge to **inform risk assessments** – defining **CQAs**, **CPPs**, **IPCs**, **PARs**, small scale studies, full scale **validation** plan.
- Sources of knowledge; scientific literature, **common industry product & platform knowledge**, specific company product & platform experience
- 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
- 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

Session 3 - 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**. The more products in the platform, the higher the chance of acceptance. Amount of knowledge available should relate to criticality.

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

Session 3 - process development & manufacturing strategy

Using **computational models** and **leveraging automation**, batch record review. Together with established acceptance criteria no need for small scale data to support column re-use.

For small molecule products, certain non-standard processes (e.g. aseptic filling, lyophilisation) for which extensive prior knowledge is available may be **justified as 'standard' manufacturing process** for a particular product / site.

(ref: EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1)

Session 3 - 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,** i.e. 3.2.A (Appendix) in this case.

Potential next steps: meeting report.. further discussion by BWP.

Session 4 – control strategy

We **already use prior knowledge**, in different forms and in different ways.. **implicit** prior knowledge

Informing criticality assessments, linking to quality **risk to safety and efficacy**

Clinical experience / relevance when setting specifications

Transparency, qualification of prior knowledge, **publication** all increase the chance of it to be accepted

Use of prior knowledge - currently implicit but can we **make it more explicit and transparent?**

Session 4 – 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

Oligonuleotides 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)

Session 4 – control strategy

Problems arising from tight specifications: batch rejections, less flexibility for shelf-life extensions, site transfers & process changes… slower patient access?

Identifying CQAs, clinical safety thresholds

Risk-based specification setting (selecting attributes and setting limits):

Clinical exposure + appropriate prior knowledge *(i.e. platform clinical and non-clinical experience)* = justified specifications

- Possibly an acceptable approach if scientifically justified but
  - Product **consistency** versus **safety and efficacy** is key
  - How will company **manage in the PQS?**
- **Prior knowledge broadens** understanding of product specific data

Session 4 – control strategy

Expanding the use of **prior knowledge** across multiple types of products

Benefit of prior knowledge in **lifecycle management** – risk assessments, variation classification, post authorisation tools (e.g. PACMP)?

Company **(applicant) experience** and **manufacturing site experience**.

Where & what in dossier? simple cross reference to other product, basic summary statistics, **graphical summary (?),** full tabular version of prior knowledge.

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.**

Session 5 – 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)

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)

What is (and isn't) considered to be prior knowledge?

- Definitions in **ICH Q8, Q10** and **EMA Guidelines** are already established and are relevant.
- **Internal knowledge**: from development and manufacturing
- **External knowledge**: Scientific and technical publications (including literature and peer reviewed publications)
- Application of established scientific principles
- Prior knowledge of **active substance**, **excipient** or **packaging**
- **platform knowledge**; platform technologies, platform design space
- 'We are not opening the door to prior knowledge. The door has been already open for some time.'
- Receiving SA from an agency should also be considered as prior knowledge (agencies have overview of all products in clinics/ on the market)

How can such prior knowledge be used in regulatory submissions?

- **identifying CQAs**, informing **risk assessments**
- informing **risk assessments,** defining **CQAs**, **CPPs**, **IPCs**, **PARs**, small scale studies, full scale **validation** plan.
- to reduce uncertainty in **risk assessments**
- Applicability / **qualification of a platform**
- **Scale up and validation**,
- Selecting **packaging** & predicting **stability**

How can such prior knowledge be used in regulatory submissions?

Risk-based specification setting:

- **Clinical exposure + appropriate prior knowledge** *(i.e. platform clinical and non-clinical experience)* = justified specifications
- Product **consistency** versus **safety and efficacy** is key

- Benefit of prior knowledge in **lifecycle management** – risk assessments, variation classification, post authorisation tools (e.g. PACMP). The company **(applicant) experience** and **manufacturing site experience** is key to the risk assessment.

How to justify its use?

- The relevance and applicability of the prior knowledge to the product under assessment must be demonstrated. i.e. the **transferability** of prior knowledge should be shown.

- 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.

How to present it in the dossier?

- Info relevant to the assessment of the MAA should be presented in the dossier – in line with Directive 2001/83/EC as amended.

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
- There is a need for **product specific assessment** in every case.
- Master files (for biologicals, excipients, packaging) are not currently possible in EU dossiers.

How to present it in the dossier?

- **Graphical summary** of prior knowledge could be an acceptable way to present the justification.
- Underpinning full data should be available to assessors to support the prior knowledge justification.
- The **justification is key**.
- Assessment decisions are based on **totality of data** (i.e. product specific data supported by prior knowledge)

Next Steps

- Publication of presentations from the workshop
- Publication of meeting report
- Follow-up discussions; BWP/QWP, interested parties, consider further guidance (e.g. Q&As)?

Concluding remarks

- Markus Goese, EBE, Roche
- Isabelle Colmagne-Poulard, EFPIA, Merck
- Keith Pugh, QWP chair, MHRA, UK
- Mats Welin, BWP, MPA, Sweden

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