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## 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

### Introduction

Prior knowledge has always been an important tool in designing both manufacturing processes and control strategies for medicinal products. In recent years, it has gained more focus in EU guidelines (e.g. process validation for biotech drug substances<sup>1</sup>; process validation for finished products<sup>2</sup>), and has been a regular topic of conversation at various conferences, symposia and meetings.

At the BWP meeting with interested parties in July 2016 a workshop on the use of prior knowledge was proposed and subsequently included in the BWP workplan 2017<sup>3</sup>. The BWP, in cooperation with the QWP, formed an [organising committee](#) of BWP & QWP members and industry representatives nominated by the interested parties to the BWP & QWP.

Making use of prior knowledge in regulatory application dossiers, to support manufacturing and control strategies, could be justifiable in certain circumstances. For prior knowledge to be used in this way, a good understanding among regulators and industry regarding the expectations of how prior knowledge should be documented in regulatory application dossiers is essential. The aim of the workshop was therefore to address what prior knowledge entails and how it can be used to support product development, manufacturing and control strategies. These general discussions were further elaborated through a number of specific industry case studies and a discussion of experiences to date of accelerated access schemes.

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<sup>1</sup> Process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014)

<sup>2</sup> Process validation for finished products – information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1)

<sup>3</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Work\\_programme/2009/10/WC500004664.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2009/10/WC500004664.pdf)



The workshop was organised into six sessions as follows:

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

The workshop was attended in person by 51 regulators from the national competent authorities / EMA and 49 industry representatives. The workshop was broadcasted live on EMA website and followed online by over 300 participants.

This report summarises the key points which were discussed during each session of the workshop. Links to the full presentation slides are included in each session. The final conclusions from the workshop are described under session 6.

## 1. What is Prior Knowledge?

Two presentations, [General considerations from regulators](#) (Mats Welin, BWP, MPA, Sweden) and [General considerations from industry](#) (Markus Goese, EBE/EFPIA/Vaccines Europe, Roche), were followed by an audience discussion.

### *Discussion*

It was noted that 'prior knowledge' is an established term which is used in ICH Q8, Q10 & Q11 and various EMA guidelines, although this term is not formally defined. Prior knowledge is an established tool that is explicitly or implicitly used for informing decisions during pharmaceutical development and lifecycle management..

The differences between common 'textbook' knowledge, internal company knowledge, external published knowledge and knowledge of regulators were discussed. It was generally agreed that prior knowledge, in the context of pharmaceutical development and regulatory applications can be :

- **internal knowledge** from a company's proprietary development and manufacturing experience (e.g. historical experience based on similar compounds, products and processes, including data modelling, application of 'platform technologies', knowledge from previous filings),
- **external knowledge** such as reference to scientific and technical publications (including vendors data, literature and peer-reviewed publications). The application of established scientific principles (e.g. chemistry, physics and engineering principles and mechanistic understanding from studies evaluating structure-function relationships) is also considered to be prior knowledge,

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.

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.

Knowledge also exists within regulatory agencies as they have sight of all products in clinical trials / on the market, however due to commercial confidentiality considerations, this knowledge is not publically available (i.e. it is not 'external knowledge'). Experience derived from this knowledge may inform regulators' assessments (e.g. answers to specific questions from an applicant during a Scientific Advice procedure) in which case it becomes part of the 'internal knowledge' from an applicant's proprietary development and manufacturing experience and can be specifically referenced by the applicant in future regulatory applications. Evolving prior knowledge may result in the establishment of new or changes to existing scientific guidelines.

The concept of master files as a tool for presenting prior knowledge was suggested by industry, in order to avoid redundant assessments. It was highlighted that an extended use of master files (e.g. for biologicals, excipients / packaging materials) is not possible under current EU legislation. If dossier content is identical to earlier submissions, the same full information (e.g. on excipients, packaging material) must be submitted within the new dossier. While it was agreed by regulators that the use of master files can avoid redundant reassessment of the same documentation in certain situations, it was noted that the master file concept alone cannot support the design of products, processes and control strategy. A challenge to the master file concept is that prior knowledge needs to be presented in the context of the application under assessment and not in isolation. Therefore, the applicability and generalisability of the provided information to the application under assessment could be more difficult to assess if the information is not integrated in the file. It was questioned whether using a master file or certificate as a record of a previous assessment was a type of prior knowledge.

It was noted that including clear references in application files to other products/procedures where the submitted information was previously submitted and assessed with a justification of the relevance of this fact to the current assessment is useful information for assessors and can help to minimize redundant reassessments, where applicable.

## **2. Using prior knowledge in product development/design**

Two general presentations, [Regulator's perspective](#) (Keith Pugh, QWP Chair, MHRA, UK) and [General considerations from industry](#) (Keith Watson, EBE/EFPIA/Vaccines Europe, Abbvie), were followed by three industry case studies (10' each) and an audience discussion.

[Case Study 1: FIM to commercial for a lyophilised \(NBE\) product](#) (Michael Siedler, EFPIA, Abbvie)

This case study presented a systematic Quality by Design approach to utilizing a technology platform for the efficient development of a lyophilized biotherapeutic drug product requiring the standardization of the formulation, the primary packaging components and the manufacturing process (e.g. lyophilization cycle).

[Case Study 2: Development of a lower dose paediatric strength IR tablet](#) (Matt Popkin, EFPIA, GSK)

This line extension case study described how prior knowledge of an existing 50 mg immediate release tablet was exploited to streamline the design and development of paediatric tablets of 10 and 25 mg strength using existing tablet granule and wet-granulation based manufacturing process (through simplified PK, scale up and control strategies).

[Case Study 3: Use of platform technologies for Adenovirus-based vaccines](#) (Mark van Ooij, Vaccines Europe, Janssen)

This case study described how an adeno vector vaccine platform, as developed by Janssen Vaccines, is using similar production process and standardised analytical testing packages; only the foreign gene inserted in the adenovirus vector backbone is different according to the targeted disease. Application of prior knowledge could allow to significantly accelerate the start of the first clinical trials in case of new disease outbreak or emergency situations.

#### *Discussion*

It was noted that prior knowledge of active substance, excipient or packaging properties from similar products can be used to support formulation design and the extent and therefore relevance will depend upon the specific nature of the regulatory submission e.g. for a new drug substance, generic or post approval variation. Concepts such as platform knowledge, platform technologies, platform design space can be used to apply such knowledge. In such cases, the applicability, or qualification, of a platform to a new molecule is a key consideration. There may be a need to adapt a product's development (i.e. 'trade-off') so that the prior knowledge remains relevant. In particular, in order to maintain the robustness and applicability of the platform, it may be necessary to exclude certain products which do not fit the platform.

The concept of 'family products' was used to describe a platform approach, for example in the setting of core CQAs/CPs. It was noted that a key use of prior knowledge is informing risk assessments and identifying CQAs. Prior knowledge from similar products can be used to characterise the link between CQAs and the QTPP. Other uses of prior knowledge include predicting issues with manufacturing scale up and stability, referring to existing extractables / leachables data and physiology based modelling.

The possible role of prior knowledge in informing the establishment of public standards and the value of product class monographs was discussed. It was noted that EDQM is currently working on developing general monographs as well as product specific monographs (e.g. Infliximab Ph Eur).

### **3. Using prior knowledge in process development & manufacturing strategy**

Two general presentations, [Regulator's perspective](#) (Seán Barry, BWP, HPRA, Ireland) and [General considerations from industry](#) (Ron Ogilvie, EFPIA/EBE/Vaccines Europe, Pfizer) were followed by three industry case studies (10' each) and an audience discussion.

[Case Study 1: Application of prior knowledge to process parameter definition](#) (Bob Kuhn, EFPIA/EBE, Amgen)

This case study presented the application of prior knowledge assessments for platform processes. Examples of systematic semi-quantitative assessment approaches were provided and an illustrative example of its application to the evaluation of a platform chromatography step. This highlighted the use of prior knowledge to separate process parameters into non-critical process parameters and potentially critical process parameters (pCPPs), enabling focus of experimental studies on aspects of the unit operating pertinent to product quality.

[Case Study 2: Validation Efficiencies from QbD & Prior Knowledge](#) (Frank Zettl, EFPIA/EBE, Roche)

This case study outlined how prior knowledge is applied through the development and validation of a monoclonal antibody molecule. Prior knowledge was generated through the comparison of multiple process parameters across 11 mAbs in order to identify critical process parameters and to support the risk assessment for the design of further validation studies of the next mAb. A proposal was also

presented as to how prior knowledge might be used to model the quality of chromatography resins over their lifetime which could reduce the burden of small scale resin lifetime studies.

With regard to case study 2 it was noted that the cross validation approach used to qualify the model is seen positive. It also was noted that a batch record review solely based on deviations is currently not acceptable.

[Case Study 3: Prior knowledge to streamline viral safety and resin lifetime studies for monoclonal antibodies and resin re-use across vaccine serotypes](#) (Marie Murphy, Eli Lilly & Company (EBE) Nancy Cauwenberghs, MSD Inc (Vaccines Europe))

This case study illustrated the prior knowledge from platform unit operations for viral reduction during monoclonal antibody purification. Experience from virus reduction during Protein A chromatography using re-used resin was presented in order to justify that virus reduction experiments using multi-cycled resin on a product-by-product basis may be obviated. Experience from virus reduction using parvovirus retentive virus filters and a panel of model viruses consisting of a parvovirus and larger viruses including a retrovirus, a herpes virus, and a reovirus or a polyoma virus was presented. Considering the size-based exclusion mechanism EBE called for feedback on the strategy to use an animal parvovirus as a worst case model for other (larger) viruses and to omit product specific validation studies with large viruses. In addition, it was suggested that, once a nanofilter has been determined insensitive to process interruption, this parameter would not have to be not tested in later virus clearance studies. The use of prior knowledge to evaluate resin reuse across serotypes of the same final product was illustrated in the vaccine case study.

#### *Discussion*

From a regulatory viewpoint it was accepted that there is potentially considerable scope for prior knowledge to be used in MAA submissions, which to date has not been fully realised. Traditionally, process development has relied on a full product-specific data package for each MAA. However it was recognised that data generated from related products can be relevant in many aspects of process development. It is important for regulators to strike a balance between the need for product-specific data and the application of regulatory flexibility where appropriate.

Many applicants have accumulated significant prior knowledge through the use of small scale studies. For many process parameters, small scale models are used to further investigate their impact on quality and thus their criticality. For similar products, the same quality attributes may be impacted by the same process parameters. Thus prior knowledge could be used to decide which quality attributes to study in these models.

Risk assessments are often used to stratify process parameters into critical and non-critical categories. In certain cases, previous risk assessments carried out for similar products may be leveraged and used in MAAs for new products. In a practical sense this means that process parameters could be justified as being non-critical on the basis of prior knowledge.

In addition to criticality designation, prior knowledge may also be useful in justifying the ranges of the process parameters. Ranges of process parameters are inputs in a manufacturing step, the outputs of which are testing of COAs. For alike products, data could be modelled to demonstrate that a certain range of a process parameter can be predicted to have a consistent impact on a certain quality attribute. Prior knowledge may be included in the justification for the set of process parameters to be challenged in product-specific small scale studies. Such product-specific studies should be aimed at confirming that the assumptions made using prior knowledge hold true for the product in question. A combination of product-specific data and prior knowledge could be used in conjunction to define the

criticality of process parameters and their respective ranges. Where prior knowledge is heavily relied on, particularly in the case of accelerated pathways, applicants should address how the data is verified post-approval. One approach could be to register a more extensive control strategy which might include additional in-process controls or release tests. At the time of approval, a post-approval change management protocol (PACMP) could be submitted as a basis for the eventual removal of these additional tests, once the relevant data has been gathered from the commercial process post-approval.

It was noted that for some classes of products, certain non-standard processes (e.g. aseptic filling, lyophilisation) for which extensive prior knowledge / experience is available may be justified as 'standard' manufacturing process for a particular product / site.

In the MAA file it is important to clearly indicate from where the prior knowledge has been drawn. It should also be explained what aspects of product-specific data prior knowledge is used to complement or substitute for, and how any remaining uncertainties arising from the use of prior knowledge will be addressed post-approval.

With regards to use of prior knowledge to streamline viral safety strategy (case study 3), it was considered that using only parvovirus during nanofiltration is acceptable for biotech products and established virus filters for parvovirus removal, noting that scientific principles and mechanism of virus reduction address the current ICHQ5A guideline, and noting that experience has been gained in CTAs and some MAAs. With regards to virus filters at low pressure/pressure release, low pressure or pressure release is considered a potential worst case parameter that could be critical under certain circumstances. More knowledge from parvovirus retention under worst case conditions is desired and product specific validation runs considering worst case conditions such as filter loading and pressure are expected.

Prior industry knowledge, as well as consortium-derived data indicate that Protein A Affinity Capture-mediated viral clearance is not impacted or slightly increases by typical resin multi-cycling.. Therefore, Antibody step yield and breakthrough of impurities could be utilised as surrogate performance attributes for resin performance over time, thus obviating the requirement to measure virus reduction using multi-cycled resin on product-specific basis. Considering the understanding of mechanism of virus reduction at Protein A Chromatography the proposal, as raised by Industry, for aged Protein A resins would be acceptable if prior knowledge has been published in scientific journals. It was noted the appropriate dossier section in which to present such prior knowledge is section 3.2.A (Appendix on adventitious agents). Regarding the vaccine example addressing resin lifetime studies, it was commented that the approach to recycle resins across serotypes of the same vaccine could be justified but highly depends on the physicochemical characteristics and composition of product intermediates of the various serotypes and merits further discussion in scientific advice.

#### **4. How to use prior knowledge in defining the control strategy**

A general presentation [Regulator's perspective](#) (R. Martijn van der Plas, BWP, MEB, The Netherlands) was followed by four industry case studies (10' each), then [General considerations from industry](#) (Andrew Lennard, EBE/EFPIA/Vaccines Europe, Amgen) and an audience discussion.

[Case Study 1: Specification Setting for a Multivalent Vaccine](#) (Nancy Cauwenberghs, Vaccines Europe, MSD Inc)

This case study illustrated the use of QC release data from multiple monovalent vaccine formulations as prior knowledge to inform the setting of specifications for multivalent vaccines. The prior knowledge included clinical experience of the former product with shared antigens and justified approval of broader specifications.

### [Case Study 2: Oligonucleotide Control Strategy](#) (Rachel Orr, EFPIA, GSK)

This case study illustrated how using an oligonucleotide synthesis platform means that consistent understanding of quality risks can drive consistent development strategies across multiple products. Prior knowledge is used to inform the concept of “populations” of impurities and to demonstrate that such impurities have equivalent toxicological impact and as such, the grouping of these impurities poses no risk to the patient, and could be considered as a basis for the control strategy. It was also proposed that there might be an opportunity to utilise prior knowledge to reduce the requirement for toxicological studies for the families of impurities due to their similarity to the parent sequence.

### [Case Study 3: Prior Knowledge in the Control Strategy for Biotechnology Products](#) (Darrin Cowley, EFPIA/EBE, Amgen)

This case study described the application of a Product Quality Attribute Assessment (PQAA) Severity scoring system for a monoclonal using prior knowledge, focusing on safety aspects of the key attributes methionine oxidation, HMW species and C-terminal variants to illustrate the various strategies used when establishing specifications. Data were presented demonstrating no meaningful change in immunogenicity for methionine oxidation or HMW species. The commonly understood ‘textbook’ prior knowledge and literature on C-terminal variants were discussed.

A model illustration was presented that incorporates clinical exposure, tolerance intervals, stability considerations and prior knowledge on product attribute and clinical exposure in setting safe, efficacious and clinically qualified specification limits. The ultimate applicability of such a model was debated and would need to be justified on a case by case basis.

### [Case Study 4: Prior Knowledge for Setting Acceptance Criteria](#) (Thomas Stangler, Medicines for Europe, Novartis)

This case study described the use of long-term variability from related processes as prior knowledge to better define the minimum needs and requirement for acceptance criteria from a manufacturing perspective. This included Bayesian statistics as a tool to incorporate process capability from platform knowledge as well as product specific data in the justification of acceptance criteria for process-related impurities and product variants. Biosimilars were also presented as an example where the reference product variability can be used as prior knowledge to justify acceptance criteria for product variants (including CQAs related to the mode of action).

### *Discussion*

It was noted that Prior Knowledge is a crucial tool in determining an effective control strategy. Usually, it is neither necessary nor feasible to investigate every aspect of a new product in a product-specific manner. Any information found can only be interpreted in the broader context of the existing prior knowledge of a certain class or family or products with similar attributes (e.g. monoclonal antibodies; oligonucleotides; subunit vaccines; enzyme replacement therapies; coagulation factor analogues). Prior knowledge can be applied to all stages of the control strategy development: CQA assessment; the testing strategy (which CQA is tested and when, or justification for not testing routinely); and for setting acceptance criteria.

For finished products containing small molecules, criticality is largely defined by the dosage form. For active substance, it is defined by the link to the finished product and process-specific impurities. For small molecules, ICH Q6A and the supporting framework (including ICH Q3 series and M7) gives a clear, risk-based framework for what acceptable limits are and the role of specifications in the overall control strategy, underpinned by shared science and risk. While it is not always easy, particularly for complex dosage forms, there is a well-developed framework.

For biologicals, it is often challenging to establish which attributes are critical and therefore to be considered when developing an overall control strategy in which risk-based approaches are required. Prior knowledge can therefore offer further insight into the assessment of criticality and/or clinical relevance of specific quality attributes.

Prior knowledge available from other molecules could be used to support the severity or criticality assessment of a given product attribute, if appropriately justified. The applicability and relevance of molecules used to provide prior knowledge would depend on the product quality attribute under consideration and its clinical context, and would require detailed and robust justification. Ranking criticality for product quality attributes identifies those attributes to be designated as 'Critical'. Prior knowledge can be used to define a set of core CQAs for a family of products (a point illustrated by the oligonucleotide case study), although care must be taken not to overlook product specific CQAs (e.g. as in the case of cetuximab, where an unexpected additional glycosylation site is present, which carried immunogenic sugar structures).

The same logic applies to identification of possible critical process parameters; where available information can support the criticality or non-criticality of a given parameter, as discussed in Session 3 (Using prior knowledge in process development & manufacturing strategy).

It was noted that any impact risk assessment of product attributes also requires a case by case consideration of the therapeutic indication, dosing regimen and patient population. The final identified risk level, incorporating prior knowledge, supports the selection of product attributes that require control in the release specification (whilst taking other specification requirements into consideration when appropriate, e.g. Ph. Eur monographs, identity testing). This approach is consistent with the principles of QbD as outlined in ICH Q8, Q9, Q11, and can apply to small molecule and biological drugs.

A justified specification (test and acceptance criterion) for a specific product should be based on a totality of evidence approach: ideally, where relevant, it is based on clinical exposure with the specific product, clinical exposure of products from the same family, together with all other pertinent scientific data (e.g. non clinical data, understanding of biology). The latter two are forms of prior knowledge, and actually add to the robustness of the justification. All case studies presented during the day in one form or the other supported the scientific validity of this point.

A robust decision is not solely based on a specific product's own data (as this data is typically somewhat limited) but on a much broader scientific basis. This was especially illustrated by the vaccine case study (where an acceptance criterion based on a few multivalent phase-III batches only would clearly ignore available, highly relevant data from monovalent products).

As an illustrative example, the setting of limits for aggregates in a monoclonal antibody (MAb) was discussed; deciding on a certain limit for aggregates for 'MAb X' is not only based on the few patients which have actually been exposed to such material, but also on many years of experience in this field of setting limits for aggregates in monoclonal antibodies.

Safety thresholds may be supported by in vitro, ex vivo or animal studies that titrate the exposure of the model system to a given product attribute (IgG High Molecular Weight species (predominantly dimer) and MetOx are provided as case studies). It is noted that the use of animal models is generally not encouraged due to 3R principle and because it is often difficult to interpret/extrapolate the obtained data to the situation in humans. Prior knowledge of qualified safety thresholds are especially useful when establishing and justifying acceptance criteria for process-related impurities, because the applicability of the prior knowledge will generally be easy to justify.



Process impurity clearance using similar processes and impurity safety data prior knowledge can be used to define specifications, and their limits, beyond product-specific clinical exposure, and can also be used to justify omission of testing for impurities in appropriate cases. Different finished products manufactured from a common active substance may use prior knowledge from the similar finished products to set product specifications beyond the clinical experience of the proposed product. Families of products with similar classes of impurity/substance could take into account prior knowledge to set purity/impurity criticality and specifications for same product class/family. Such an approach avoids the consequences of overly tight specifications, restricted to product specific clinical exposure and which may result in rejection of otherwise safe and efficacious batches or determination of an unnecessarily short shelf-life/expiry date. This especially applies to accelerated programs or breakthrough therapies, where limited data may be available.

For certain products (e.g. small molecule products) depending on the particular parameter, specification limits are often initially set based upon batch consistency. It was discussed whether, for complex biological products, acceptance criteria for certain attributes could be dissociated from batch consistency.

It was agreed that further discussion of the idea that, for certain attributes where safety and efficacy thresholds can form a basis for specification setting, batch consistency evaluation could be dissociated from setting product attribute specification limits, would be useful. Specification setting should follow a risk-based assessment approach linked to product safety and efficacy.

Prior knowledge is currently often used implicitly while it is necessary to identify the prior knowledge more explicitly if and when it is used. With regards to presentation in the MAA dossier, it was noted that Prior Knowledge should not be presented in isolation, but always in the relevant context (in this case especially S.4.5 and P.5.6); scientific papers should be quoted and copies provided as appropriate; if in house knowledge from related products is used, the data and source should be identified as appropriate. It remains the responsibility of the Applicant to provide in S.4.5 and P.5.6 a full, data and science driven justification for both the choice of tests and the acceptance criteria. This justification will usually include both prior knowledge and product specific data.

## **5. Experiences of accelerated access approaches (i.e. PRIME)**

Two general presentations, [Regulator's perspective & experience on prior knowledge and accelerated access](#) (Veronika Jekerle, EMA, BWP secretariat) and [Considerations for Accelerated CMC programs](#) (Ronald Imhoff, EBE, Janssen / Richard Keane, EBE, Biogen) were presented followed by two industry case studies and a panel discussion.

[Case Study 1: Atezolizumab: A Case Study of Accelerated Development](#) (Andrea Challand, EBE, Roche)

The case study presented experience from US-FDA on the development and submission of a Biologics License Application (BLA) for a "Breakthrough Therapy" designated monoclonal antibody targeting PDL1 (Atezolizumab). Several acceleration opportunities were realised resulting in a 19-months gain versus a standard development timeline (i.e. qualification of the scale-down model, approach for DP validation with Phase III material, co-validation approach for method transfer, prior knowledge-driven risk assessment to inform the control strategy and process characterization studies). A summary document listing platform knowledge derived from 8 mAbs together with examples of risk ranking and filtering was included in the dossier.

[Case Study 2: Avelumab integrated Mab example](#) (Isabelle Colmagne-Poulard, EFPIA, Merck)

This case study illustrated the integration of prior knowledge within the entire development and submission of a second PD-L1 monoclonal antibody under accelerated pathways, i.e fast track and

breakthrough therapy designation in the US, and conditional approval in the EU and exemplified documentation of prior knowledge within the CTD and possible use of regulatory tool (e.g. Post-approval change management protocols (PACMP)) to accelerate the original submission or anticipate and further downgrade planned life cycle changes implementation.

Panel Discussion:

- Peter Richardson, EMA, Head of Quality (Panel Chair)
- Sol Ruiz, BWP chair, CHMP, CAT, AEMPS, Spain
- Nanna Kruse, BWP vice-chair, CAT, DKMA, Denmark
- Marie-Hélène Pinheiro, EMA, Industry Stakeholder Liaison
- Jordi Llinares Garcia EMA, Head of Scientific and Regulatory Management Department
- Ronald Imhoff, EBE, Janssen
- Richard Keane, EBE, Biogen
- Mairéad Duke, EBE, BioMarin

### *Discussion*

Accelerated access approaches such as PRIME in the EU are reserved for medicines that can demonstrate, based on early clinical data, a major therapeutic advantage over existing treatments or benefit patients without treatment options. Such approaches usually demand a shortening of Quality/CMC development timelines resulting from clinical acceleration and reduced assessment time. Indeed, experience with PRIME products in the EU to date has demonstrated that quality aspects are commonly raised and discussed during the development phase for PRIME designated products and benefit from an early focus in order to avoid delays during the marketing authorisation application procedure and thus defer access to patients.

The use of prior knowledge to support product development, process design and control strategy was welcomed by both regulators and industry. It was emphasized that prior knowledge needs to be made visible to Regulators and included as part of the MAA dossier (e.g. in form of a summary) in order to be considered during the assessment of the specific product. For example, where prior knowledge has been assessed as part of a Scientific Advice procedure, the Final Advice Letter from the CHMP should be part of the MAA dossier (in module 1) and the specific prior knowledge should be incorporated into the relevant MAA dossier sections in module 3. In addition, the relevance and application of prior knowledge to the product in question may be discussed between Industry and Regulators as soon as possible (during PRIME kick off, Scientific Advices or pre-submission meetings) to allow for better integration of prior knowledge into the CMC/Quality strategy, planning and compilation of the submission dossier.

Clarity on the use of prior knowledge can help to direct limited Company time/resource to those areas within the quality development that may not be deferrable to the post-authorisation phase.

It was also highlighted that prior knowledge can help justify greater flexibility in the compilation of quality data in relation to the approval timeline, allowing some quality data to be deferred on a risk-proportionate basis into the post-authorisation phase. The risk could be mitigated through an additional layer of control measures (e.g. manufacturing & product controls) or increased planning for data submission (e.g. PACMPs, recommendations and other follow-up measures) until the expected data set has been acquired. The level of detail included in the regulatory dossier (versus present in the PQS) should be commensurate with the risk to product quality and clinical benefit-risk..

In order to support accelerated access approaches, Regulators in collaboration with Industry could further explore options or mechanism to facilitate update and re-use of prior knowledge across

regulatory submissions (IMPD/MAA) of multiple products, as long as the relevance of the data package has been agreed with Regulators and is included in the actual CTD submission.

## 6. General discussion, summing up and way forward

The lessons learned from the workshop and next steps were summarised in a presentation at the end of the meeting, [General discussion and meeting conclusions](#) (Brian Dooley, EMA, Quality Office) followed by concluding remarks from Mats Welin (BWP, MPA, Sweden), Keith Pugh (QWP chair, MHRA, UK), Markus Goese (EBE, Roche) and Isabelle Colmagne-Poulard (EFPIA, Merck).

The key conclusions from the workshop are summarised below:

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

Prior knowledge is an established concept that is clearly referenced in ICH Q8, Q10, Q11 and EMA guidelines. There are differences between common 'textbook' knowledge, internal company knowledge, external published knowledge and knowledge of regulators.

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.

Experience derived from regulators' knowledge may inform regulators' assessments (e.g. answers to specific questions from an applicant during a Scientific Advice procedure) in which case it becomes part of the 'internal knowledge' of an applicant. Common textbook knowledge is not considered to be prior knowledge in the context of the discussions and examples explored in this workshop, as it is publically available and generally accepted knowledge which doesn't normally require further elaboration or justification for use.

### ***How can such prior knowledge be used in regulatory submissions?***

Prior knowledge is commonly used for informing decisions during pharmaceutical development and is therefore, directly or indirectly, explicitly or implicitly, included in planning for new products, manufacturing changes and specification setting. Medicine 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-Q12.

Examples of how prior knowledge can be used which were discussed during the workshop include;

#### *Risk assessments*

Prior knowledge can be used to inform risk assessments during product and process development and in defining a control strategy. For example in defining CQAs, CPPs, IPCs, and PARs; assigning criticality and linking PPs to CQAs; setting acceptable ranges for CQAs; designing small scale studies and full scale validation plan. Prior knowledge can be used to reduce uncertainty in risk assessments, e.g. uncertainty in detectability and occurrence scores.

### *Platform technologies*

Prior knowledge can be used in synthetic process design, predicting drug substance physical properties, platform formulations (i.e. dosage forms, excipients, manufacturing process). Prior knowledge could be used to justify classifying certain process parameters as non-CPP for next products which promote focus on those parameters which are relevant for product quality

### *Risk-based specification setting*

Where relevant, prior knowledge from (platform) clinical and non-clinical experience with other products and understanding of biology can be used to supplement product specific clinical exposure data to support a justified specification (test and acceptance criterion) as part of a totality of evidence approach.

### *Lifecycle management*

There is a clear use for prior knowledge in lifecycle management – informing risk assessments, assigning criticality, linking risk to variation classification, post authorisation tools (e.g. PACMP). The applicant and manufacturing site experience is always a key part of risk assessments.

### ***How to justify its use?***

Prior knowledge is indispensable because it provides extensive additional information and assurance beyond product specific information. Transparency through the use of publicly available information (peer reviewed scientific publications; public technical reports; compendia) is strongly preferred, and stakeholders are invited to promote and cooperate with the sharing of knowledge. However, it is acknowledged that company specific (especially manufacturing site specific) knowledge may not be amenable to this approach.

There was general agreement that the applicant must justify the relevance and applicability of the prior knowledge for each specific new product under review. The applicant's own experience and manufacturing site experience is a key aspect in doing this.

There is a need for product specific assessment in every case. The justification for the use of prior knowledge is always key. 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. It is not expected that prior knowledge is repeatedly reassessed, however, the context and justification in each case needs to be made.

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 included.

The EMA encourages submission of prior knowledge in scientific advice applications and MAA files where appropriate. Applicants are encouraged to discuss the appropriateness and extent of use of prior knowledge with the EMA early in development (i.e. in scientific advice and other pre-submission activities) in order to agree on the best way to present prior knowledge in the MAA dossier. It was noted that the Scientific Advice procedure was a reliable way of getting clear regulatory feedback on the use of prior knowledge during pharmaceutical development.

### ***How to present it in the dossier?***

The information relevant to the assessment of the MAA should always be presented in the dossier, in line with Directive 2001/83/EC, as amended. Prior knowledge is currently often used implicitly, and it is necessary to identify the prior knowledge more explicitly if and when it is used. With regards to

presentation in the MAA dossier, it was emphasised that prior knowledge should not be presented in isolation, but always presented and discussed in conjunction with the product-specific data in the relevant context and in those CTD sections where it is used to support certain claims; e.g. justification of specification or manufacturing process development.

It was agreed that the acceptability of reproducing full / part information, and/or cross references to previous assessments depends on the intention of the study (e.g. to support early formulation development or late stage commercial formulation changes).

Scientific papers should be quoted and copies provided as appropriate. If in-house knowledge from related products is used, the data and source should be identified as appropriate and differentiated from product specific data. Tabular presentations are preferred for data which are amenable for such an approach: graphical presentations (in addition to, or instead of tabular data) are useful, especially for large datasets.

Prior knowledge could be presented in supportive dossier sections (3.2.S.2.6, 3.2.P.2, 3.2.A, 3.2.R) and, where relevant in module 1 (Scientific Advice letters, pre-submission meeting minutes (if appropriately flagged for assessor)) For assessment decisions to be made based on totality of data (i.e. product specific data supported by prior knowledge), the prior knowledge needs to be visible and readily accessible to assessors in the application file and the underlying full data package should be available upon request. It is acknowledged that as the extent of prior knowledge data may be large, the data should be summarised in a clearly understandable way. A discussion of how the prior knowledge data is to be used should be integrated with the relevant product-specific data to provide an overall understanding of product development and control. Extended use of master files (for biologicals, excipients, packaging) are not currently possible in EU dossiers.

### **Next Steps**

The meeting report will be presented to the BWP and QWP for information.

The possibility for follow-up discussions, e.g. at BWP/QWP interested parties meeting, or developing further guidance (e.g. Q&As) on the topic of Prior Knowledge will be considered by BWP and QWP.