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

Subteam 5
Experiences of accelerated access schemes (PRIME/adaptive/accelerated pathways)
GENERAL CONSIDERATIONS

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London, Nov. 23, 2017

efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

Considerations for Accelerated CMC programs- EBE/EFPIA

- **Accelerated access** (e.g. PRIME, accelerated assessment, conditional assessment) demands a **shortening of development timelines**, and the need to ensure the CMC development can keep pace with the clinical programme acceleration.
- **Prior knowledge can help support CMC strategy and flexibility in data requireme**nts, hence timelines, by providing supporting evidence **for assurance of quality** without impact on risk /benefit balance
- This strategy must also **assure the predictability** needed to deliver reliable access/supplies of product to patients, by better planning of reporting of data
- **Practical solutions for dossier requirements** have been proposed for further discussion (e.g. how to capture dynamic concept of prior knowledge in dossier structure, level of details etc.)

Leveraging prior knowledge to accelerate dev. pathways

Knowledge as an important source of data/modelling to accelerate development timelines

- **Leverage product and/or platform knowledge**
  - *Risk assessment/mitigation activities – Ex: Setting of CQAs, CPPs and non-CPPs, streamline PC*
  - *Scientific justification – Ex: establishment of quantitative criteria as part of CS, ranges*
- **Frontload CMC dev. Activities and focus on unknown**
  - *Allow to concentrate on activities needed to address non-platform behavior, non-standard process and/or unusual product characteristics and characterization*
- **Source of information for strategic decision-making**
  - *Design – Ex: choice of formulation, choice of unit operations and process flow*
  - *Comparability assessment*

Knowledge as an important regulatory tool to allow predictability

- **Leverage prior knowledge from comparable development or clinical phase materials**
  - *Delay process optimization to post approval*
  - *Life cycle management through PACMP*
- **Use of prior knowledge to enhance planning and predictability in timelines**
  - *Defer supply of data – Ex: Stability commitment through use of supportive stability data, on-going PV protocols, PPQ and extrapolation of stability data as in small molecule*
  - *Waiving of data – Ex: PPQ batches when sufficient prior knowledge + dev. and small scale evidence*
  - *Communication tool – e.g ICH Q12 LCM plan to present and plan activities regarding future supply*

How to document prior knowledge in regulatory dossiers

Level of details needed

Use of prior knowledge		Regulatory file content
Establishing quantitative quality criteria or supporting critical aspects of CS	Data	Summary of data applied, and justification of applicability.
Justification of scientific conclusions and support of risk assessments	Criticality	Brief summary of knowledge applied and justification, details commensurate with risk and extent of use. Additional details available in PQS
Strategic choice	Knowledge	Included only if needed to illuminate critical strategic decision.

Capture of prior knowledge in dossier lifecycle

Static

Dynamic

Regulatory tools (ex.)

- SA minutes (Module 1)
- Relevant CTD section(s) *32S(2.6), 32P, 32A1 (platform knowledge) & 32A2 (viral safety strategies), 32R*
- PACMP (32R)
- Option for Master File (Living document)

Inspection

- PQS

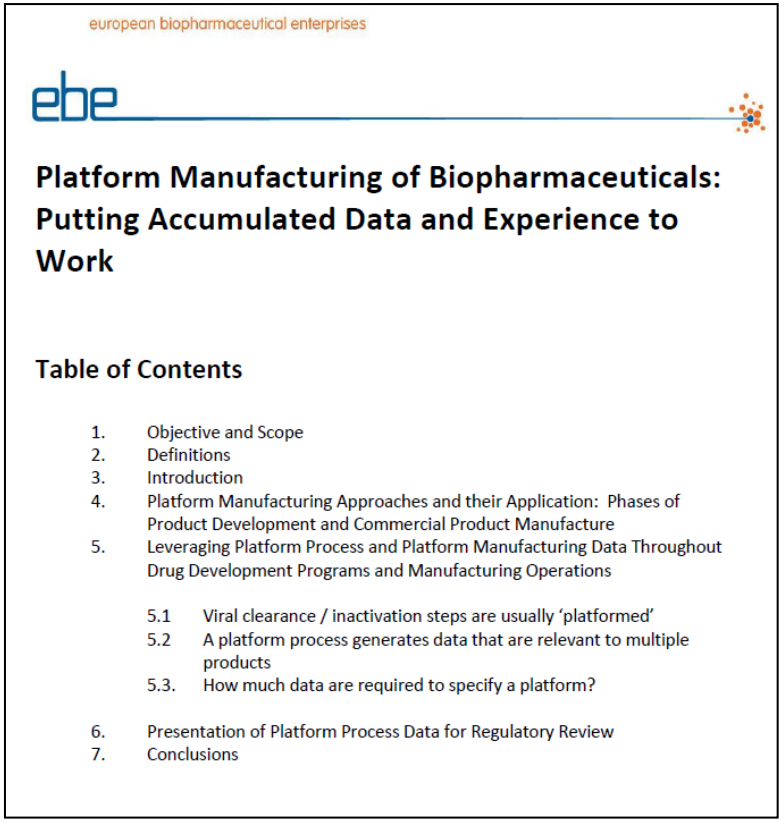
Need to ensure flexibility in reporting : Established conditions vs supportive knowledge

Recommend flexible approach to how prior knowledge could be presented

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

ebe

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

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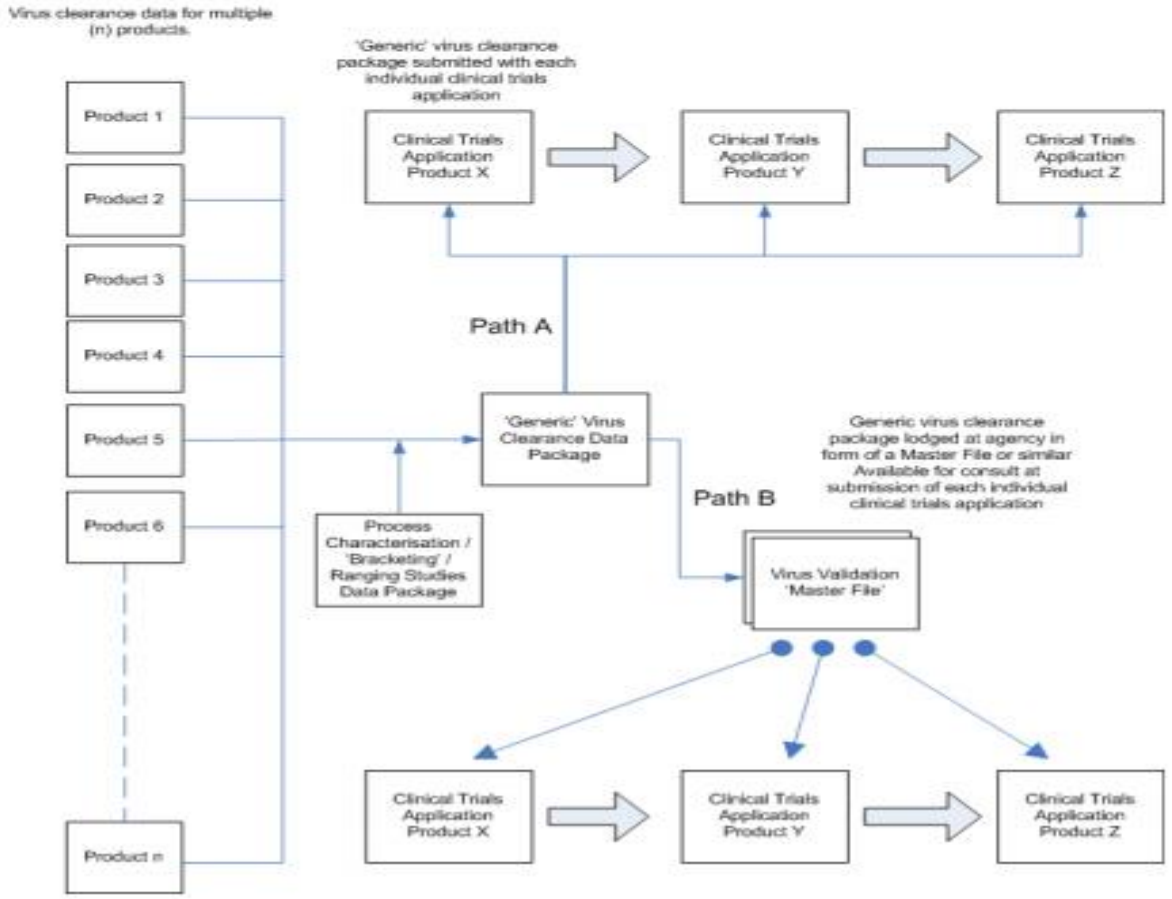
Figure 4 **Possibilities for presentation of platform-derived data for regulatory review. A 'generic' virus clearance data package is shown as an example, but this illustration could apply to any package of platform process data. Data could be presented for review by submitting the same data package with each new clinical trials application (Path A) or presented once to the agency to be maintained as a type of 'Master File' (Path B). The principles shown could equally be applied to Marketing Authorisation Applications.**



Prior Knowledge in Regulatory Submissions

Current issues in using relevant prior knowledge:

- Cross-reference to existing prior knowledge in other submissions is not currently allowed (for ex. device, excipients, analytical methods and other common parts of the Dossier)
- Re-submission of the prior knowledge from other, approved dossiers leads to re-review and new questions on already-approved data

Approaches to facilitate the use of prior knowledge:

- A mechanism is required to ensure prior knowledge can be used to support the dossier. Essential requirements include:
  - The non-product specific prior knowledge would be clearly defined (ex. Platform knowledge), and the relevance for a specific product justified in CTD
  - That prior knowledge information may be used to support multiple purposes i.e IMPD, MAA, Variations, Art.58
  - That such prior knowledge would not be re-reviewed or only when referenced in an application
  - That such information is maintained up-to-date by holder and capture dynamic evolution of prior knowledge available to inspectors (and assessors on a defined frequency or upon submission of a particular application)
  - That such prior knowledge is available for use in multiple submissions
  - That it allows to provide confidential information to another Party and therefore requires authorization to incorporate by reference any such prior knowledge information in a file

Summary of Key messages for session 5:

- **Need opportunities to agree early** in accelerated pathways, how companies intend to leverage prior knowledge (i.e. prior to extensive product specific data availability)
  - Could learnings from PRIME be more broadly applicable
    - For example access to Rapp. national scientific advice and/or use of modality 'experts'
    - For example access to PAT or BWP in forum other than Scientific Advice
- **Need for leaner process in the context of accelerated pathways, for early decision process**
  - Facilitate proactive, continued and strengthened dialogue in accelerated pathways (including PRIME, adaptive pathways and related procedures i.e accelerated assessment and conditional approval), with Inspectors & Assessors, with decisions captured.
  - Increase use of protocols (PPQ + CPV) or increased use of supportive stability data at time of submission and defer/waive data reporting (during review/at time of inspection/post authorization)
  - Options for 'Rolling submission', including where prior knowledge data may be used at submission and actual data could be added during review or as POC
- **Recommend a flexible approach/options to how prior knowledge is presented in the submission:**
  - Level of detail commensurate with risks and context of use of prior knowledge
  - 'living Master File' or similar mechanism to capture prior knowledge and cross refer to it for the purpose of multiple submissions

Industry presentations:
Case studies

- Atezolizumab: A case study of accelerated development
  - Andrea Challand (Roche)

- Avelumab integrated Mab example
  - Isabelle Colmagne-Poulard (Merck)

Backups

Overview of current Master File use

ASMF	DMF	JAPAN MF	CANADA MF
Chemical and herbal active substances*	Type I - Obsolete (manufacuring site, facilities, SOPs, and personnel) Type II – DS, DS intermediate and material used in preparation or DP Type III – Packaging material Type IV – Excipient Type V – FDA accepted reference information – requires FDA clearance (ex. manufacturing site, facilities, SOPs and personnel for sterile plants, production of gene or cell based therapies for CTs, CMO facilities in support of BLA or BLA supplements, single shared system for REMS)	Active substances, intermediates, pharmaceutical product materials, excipients, premix, materials for MDs and packaging materials	Drug substance or intermediate (such as active substance, vaccine Ags, excipients of biological origin, adjvants - type I), CCS or components (type II), excipients, colorants, flavors and additives including alum and growth media (type III), dosage forms and DP intermediates (type IV

Overview of DMF - US

- There is no legal or regulatory requirement to file a DMF.
- The information contained in the DMF may be used to support an IND, an NDA/BLA, another DMF, an export application, or amendments and supplements to any of these.
- The DMF is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.
- A DMF is not a substitute for an IND, a NDA, or an export application.
- It is not approved or disapproved.
- Technical contents of a DMF are reviewed only in connection with the review of an IND, an NDA, or an export application when referenced is those applications.
- When an applicant references its own material, the applicant should reference the information contained in its own investigational drug or marketing application directly rather than establishing a new DMF.
- The holder should provide an annual report on the anniversary date of the original submission of the DMF.
- Failure to update changes made by the DMF holder beforehand can cause delays in FDA review of investigational drug or marketing application or any amendment or supplement to such indications.
- FDA Guidance on Drug Master Files (1989)