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

Subteam 5 –

Experiences of Accelerated Access Schemes

Case study #1: Avelumab integrated Mab example

Isabelle Colmagne-Poulard (Senior Dir. Regulatory CMC/ Merck)

EMA workshop - London, Nov. 23rd 2017

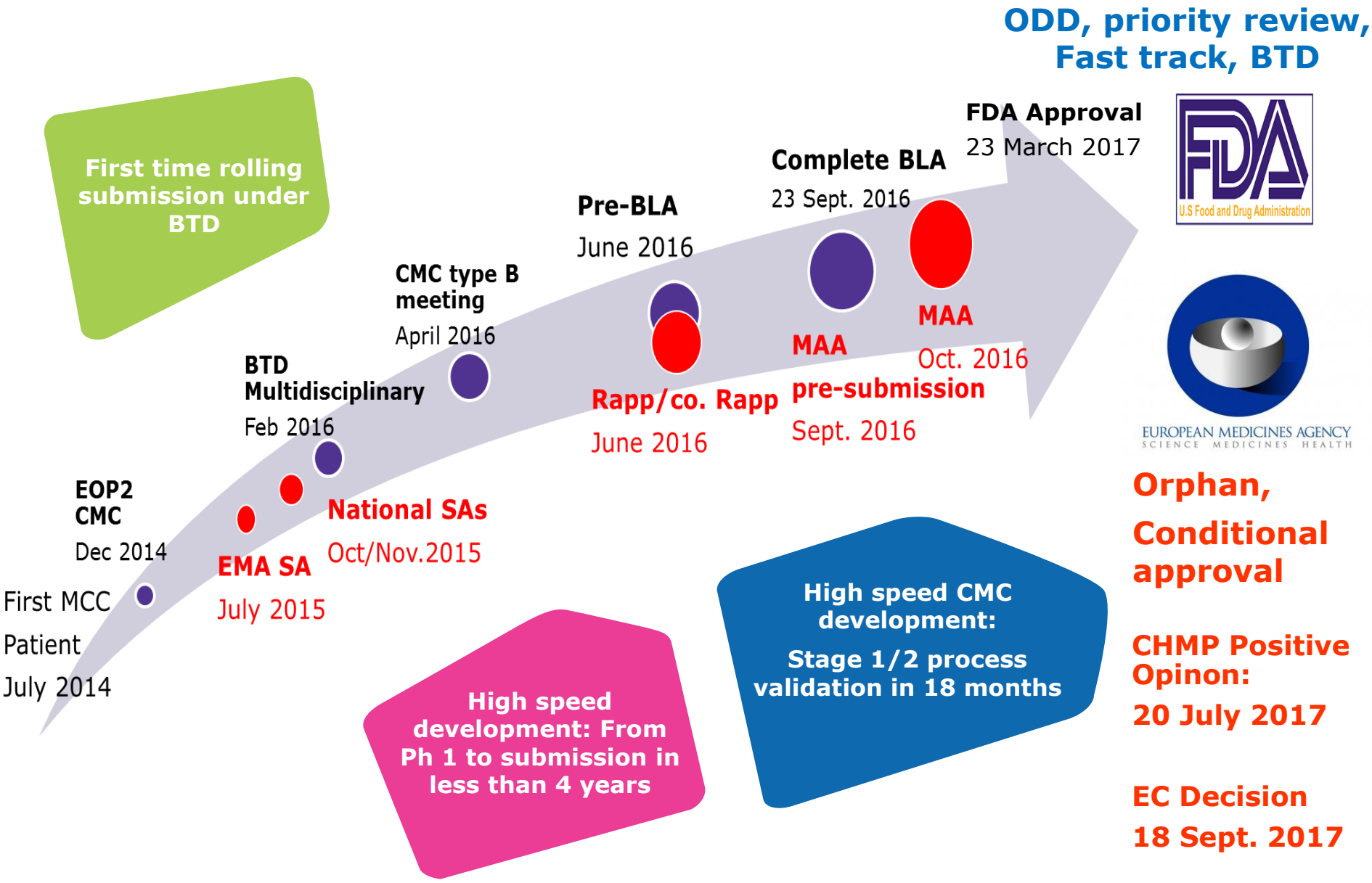
efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

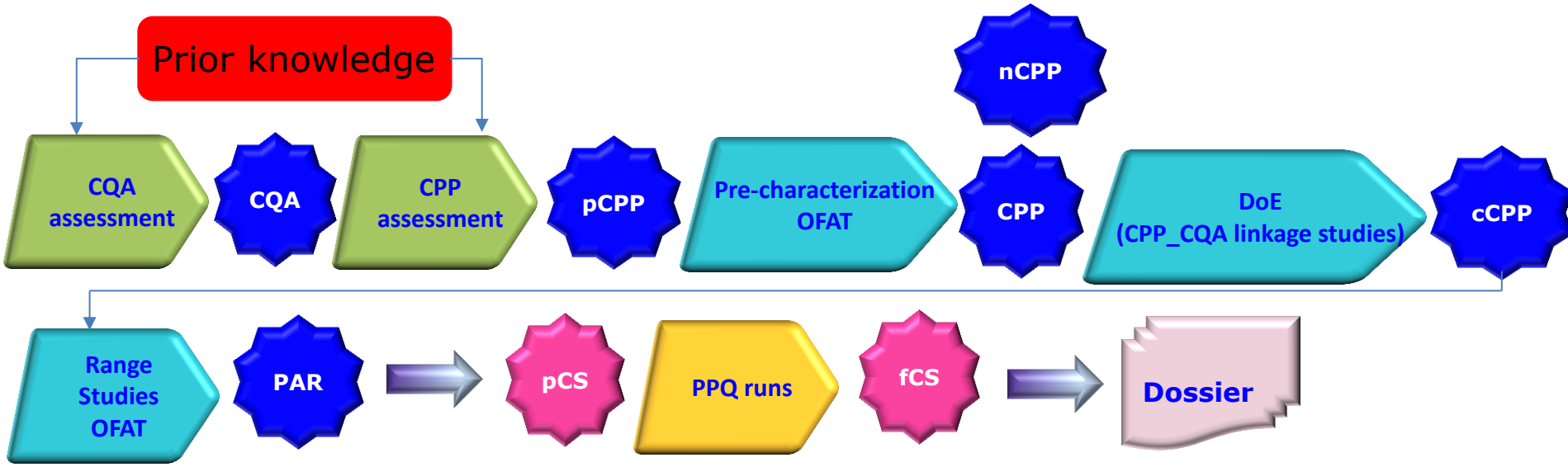
Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

Anti-PD-L1 (avelumab) Regulatory Journey



QbD – Setting Process understanding

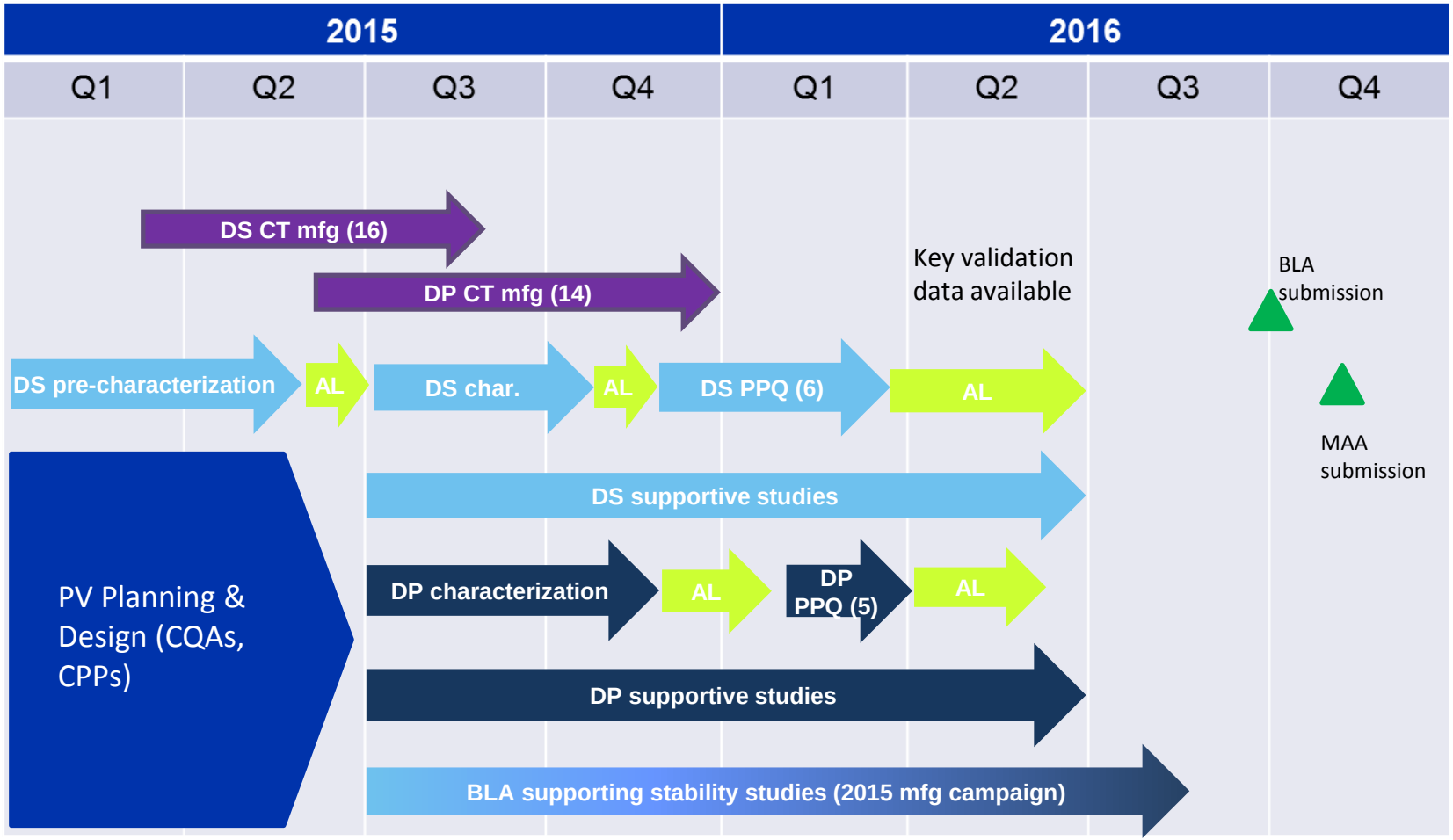


QTPP	• Establish Quality Target Product Profile prior to process development activities
CQAs	• Identify critical quality attributes (CQAs), linking QAs to clinical safety and efficacy – criticality assessment
Risk assessment (Quality – Process)	• Link process parameters (PPs) to CQAs on the basis of prior knowledge and process development experience ⇨ pCPPs
Process characterization	• Evaluate process parameter ranges as part of pre-characterization • CPP-CQA Linkage studies
Risk assessment (Quality – Process)	• Reassess and confirm criticality of PPs based on process characterization • Range studies to determine PARs
Process Control Strategy (PCS)	• Design and implement a control strategy – e.g. linking CQAs to process capability and detectability

Accelerated Validation plan

All Validation package in 1.5 year

Overall time saving from prior knowledge ≈ 6 months



QbD elements – Product relevant CQAs

CQA identification

Prior knowledge

Literature, prior clinical experience

1 Selection of pCQAs

- Exhaustive list and assessment of impact of a variation of a QA on biological activity, PK, immunogenicity and safety defined for the same class of product (IgG1)

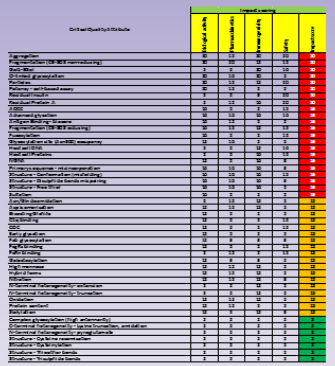
Summary Submitted

2 Selection of product-relevant CQAs

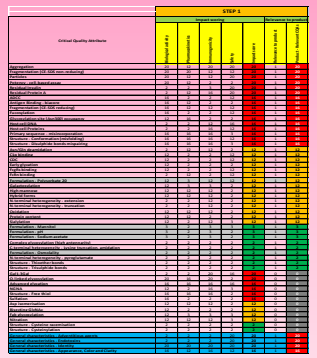
- Reassessment of same class pCQAs based on specific product characteristics or expression system and mechanism of action
- Output: CQAs classified in accordance with their degree of criticality

Summary Submitted

IgG1 pCQAs



Product specific CQAs



QbD elements – Product relev

PQS
Justification of risk scoring, based on prior knowledge

CQA identification

Prior k

- a
- v
- bi
- im
- defi
- prod

their
of criticality

Summary Submitted

Summary Submitted

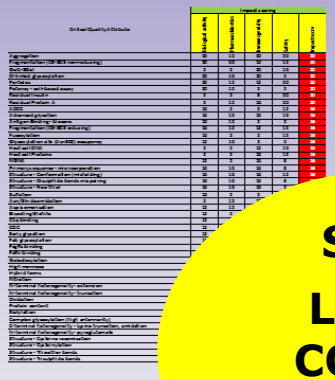
The general approach was considered acceptable;
However, the cut-off assigned to some CQAs was challenged during national SA based on potential consequences on patients

How can prior knowledge be presented and maintained so as to decrease the level of details needed for justification of risk scoring in regulatory submission

(Q&A EMA/59240/2014 and EMA/CHMP/BWP/187338/2014)

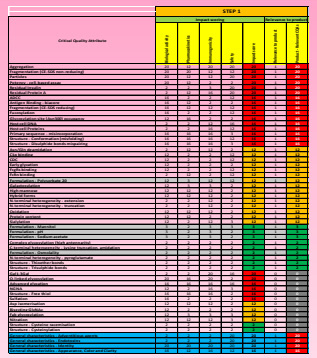
«It is up to the applicant to determine what RA are included in the submission. the level of details should be commensurate with the level of risks»

IgG1 pCQAs



S.2.6
List of CQAs + General approach

Product spec CQAs



QbD elements – Platform relevant CPPs

CPP identification

Prior knowledge

(literature, platform knowledge) activities

Development

1 Selection of PPs

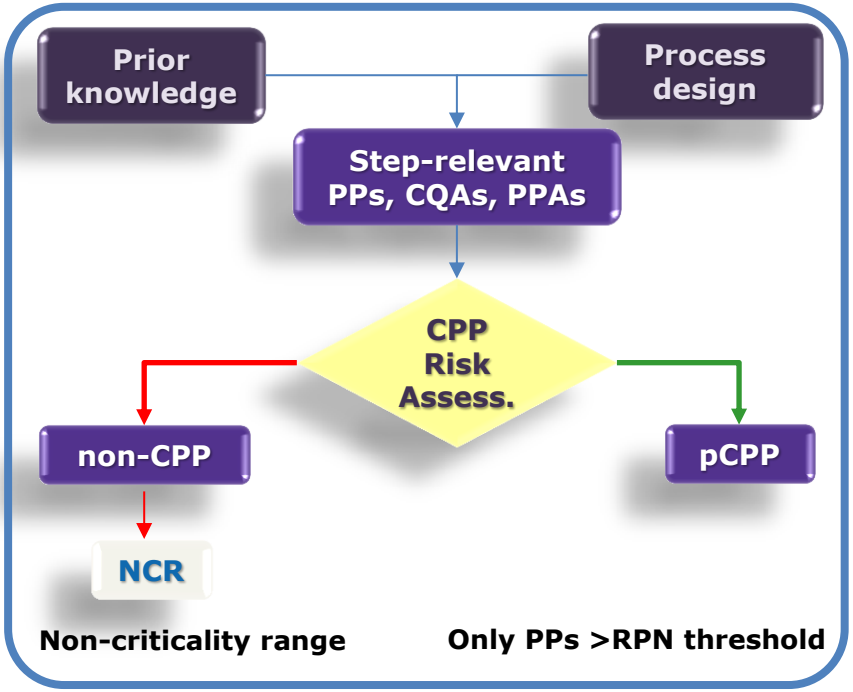
- Exhaustive list and assessment of impact of a variation of PP on CQA based on prior expertise gained from similar expression system, manufacturing process and cl... produc...

PQS knowledge management

2 Selection of relevant pCPPs

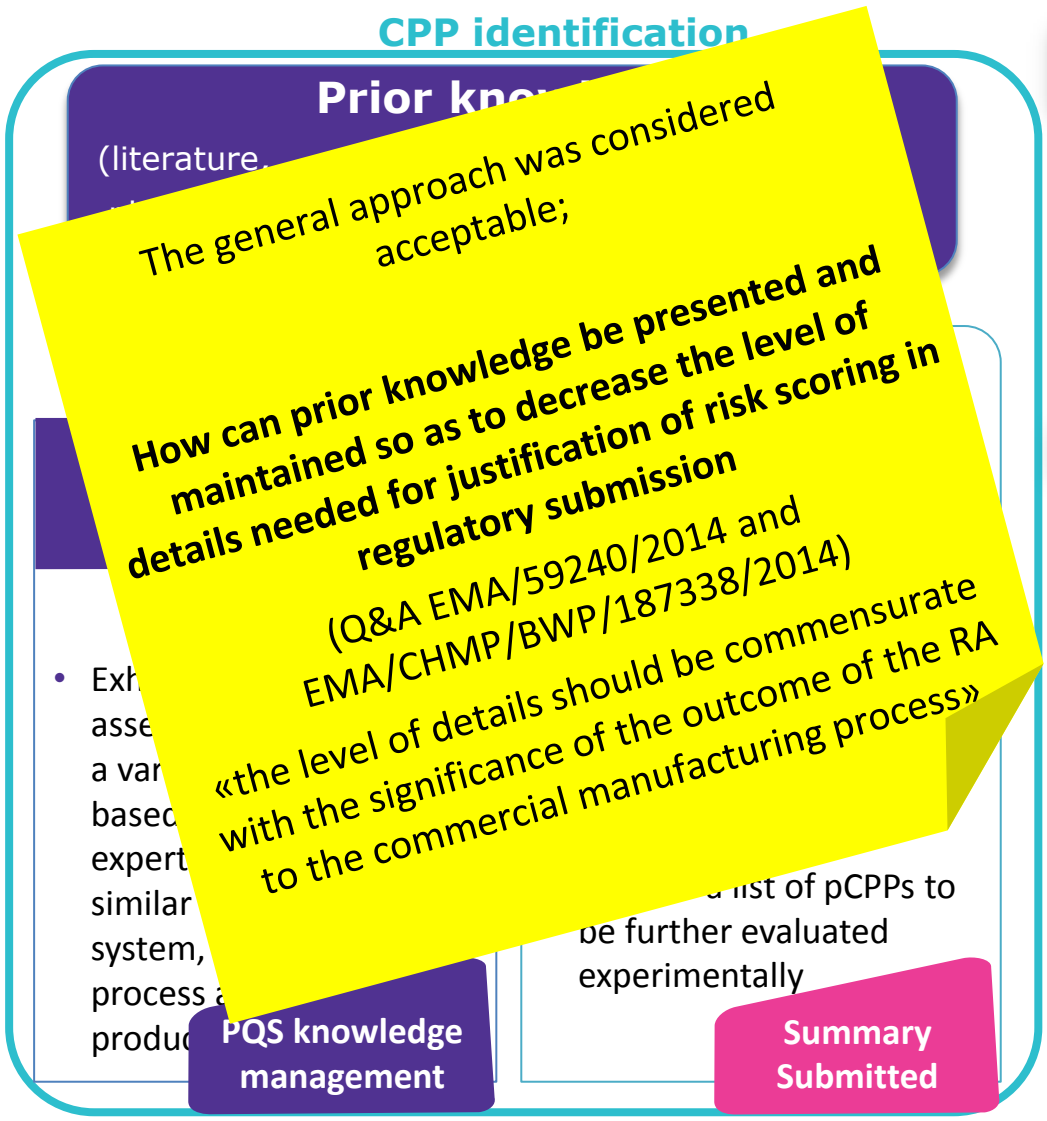
- Mapping of manufacturing steps and PPs
- Mapping of CQAs potentially impacted in each step
- Risk ranking
- Output: a list of pCPPs to be further evaluated experimentally

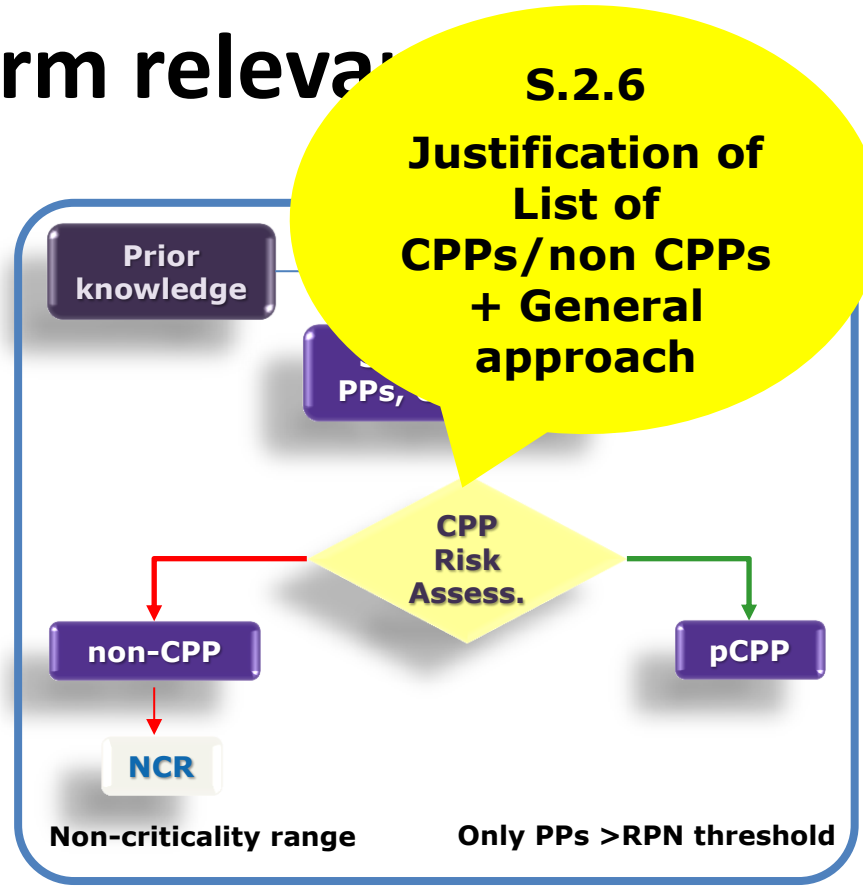
Summary Submitted



Pre- Characterization studies

QbD elements – Platform releva





Pre- Characterization studies

Elements of integrated Control Strategy

3 Process characterization

- Experimental evaluation of step-relevant potential CPPs that affect step-relevant CQAs
- Output: Confirmation of step-relevant CPPs

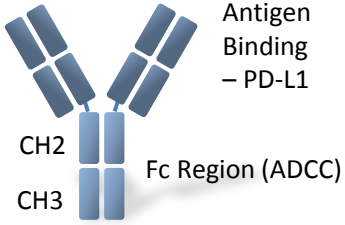
Submitted

4 Process capability and Detection

- Assessment of the capability of the process to control CQAs
- and analytical panel to detect a variation of a CQA
- Output: preliminary Control Strategy

Submitted

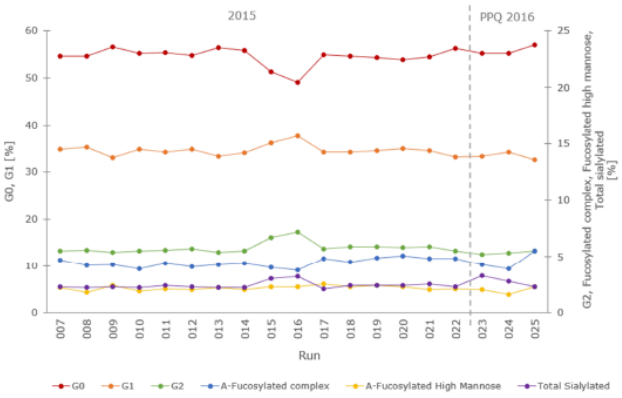
Control Strategy – Fc effector function

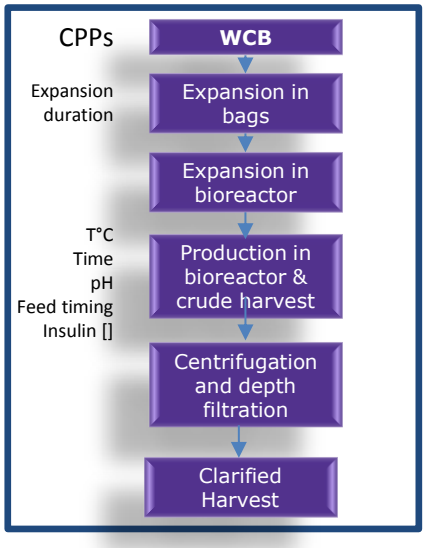


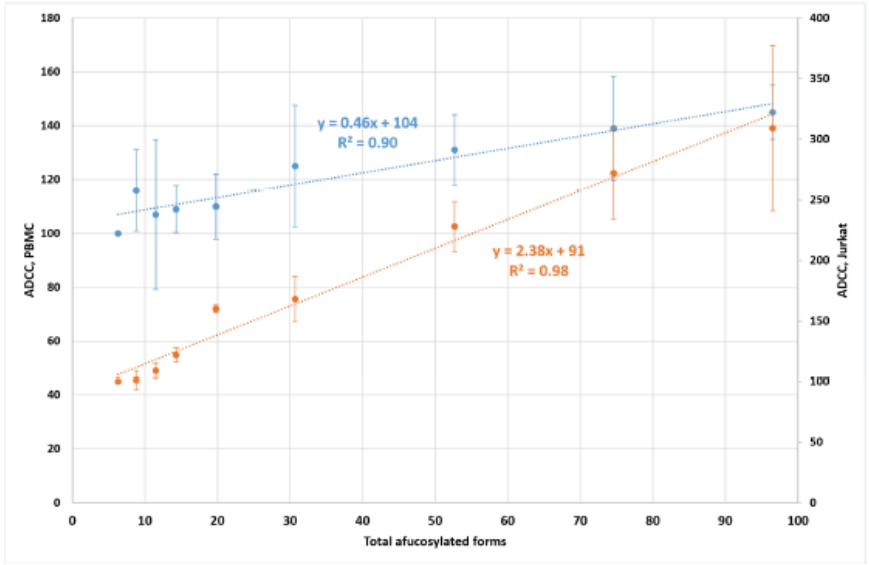
Prior knowledge (Lit.)
Afucosylation → ADCC

Applicability of Prior knowledge

- **Dev. on Small scale model**
  Induction of afucosylated form and experimental spiking with DS to obtain various amounts tested for binding to FcγRIII by biacore and ADCC assay using PBMC and Jurkat cells
- **Not tested in PC**







Process capability

- **Clinical manufacturing:**
  glycosylation remained consistent across DS batches
- **Process characterization and range study:**
  glycosylation-related CPPs with associated PARs are controlled during cell culture process

Control Strategy

- **CMAs**
  Cell culture medium & main feed variability may impact glycosylation
- **CPPs**
  Culture step was determined as last step impacting fucosylation
- **Testing Controls**
  Fucosylation test (glycan mapping) is performed on DS as a surrogate to ADCC

Control Strategy – Fc effector function

Justification in S.2.6 (CS) + detailed in SA Briefing book

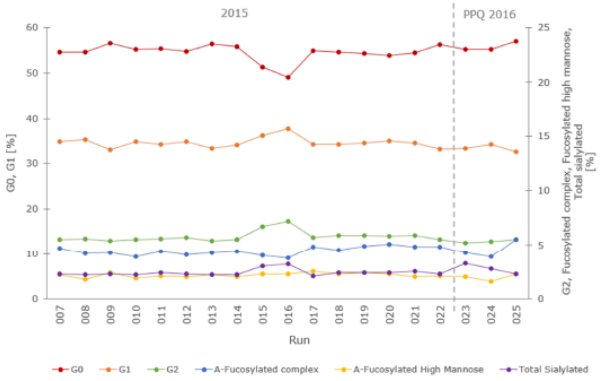
CH3

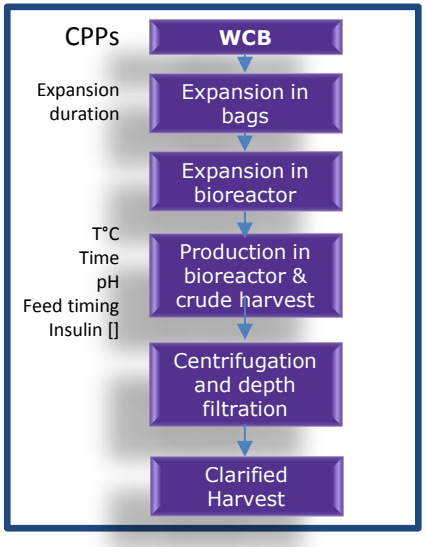
Prior knowledge (Lit.)
Afucosylation → ADCC

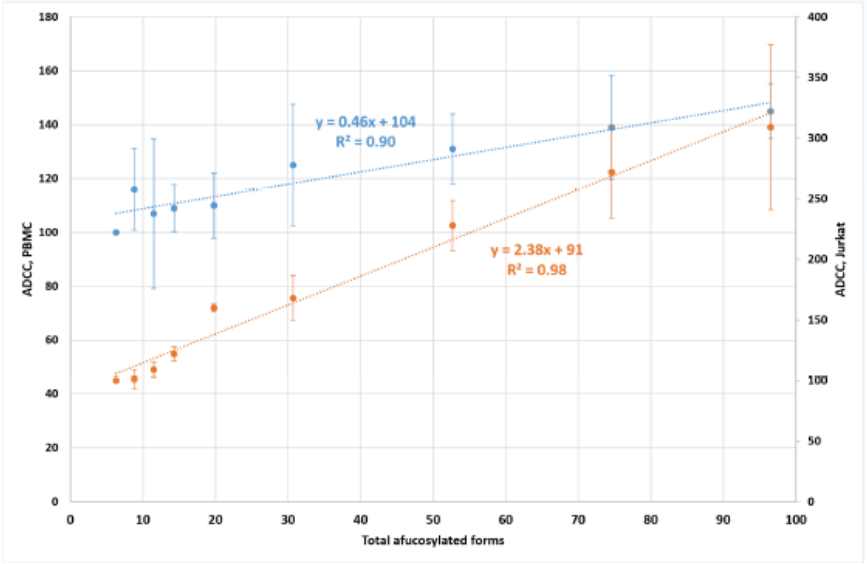
ability of knowledge

. on Small scale model
nduction of afucosylated form and experimental spiking with DS to obtain various amounts tested for binding to FcγRIII by biacore and ADCC assay using PBMC and Jurkat cells

- **Not tested in PC**







Process capability

- **Clinical manufacturing:**
  glycosylation remained consistent across DS batches
- **Process characterization and range study:**
  glycosylation-related CPPs with associated PARs are controlled during cell culture process

Control Strategy

- **CMAs**
  Cell culture medium & main feed variability may impact glycosylation
- **CPPs**
  Culture step was determined as last step impacting fucosylation
- **Testing Controls**
  Fucosylation test (glycan mapping) is performed on DS as a surrogate to ADCC

Process Validation Approach

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Process Evaluation

Process Verification

Ongoing Process Verification

- **Extensive number of DS and DP batches generated for clinical use and consistent with Process Verification batches**
  - Dev. Product (Process A) used in nonclinical, Phase I and MCC pivotal study: > 40 batches
  - Clinical product (Process B) used in Phase I, MCC confirmatory study and other indications: > 20 batches with commercial process/equipment/Sites
  - Analytical Comparability demonstrated between Process A and B materials

Although supported in MS SAs but considered «challenging» in the context of an accelerated assessment, «continous process verification» (stage 1) data were ultimately not considered as alternative approach to prospective process verification

→ **3 DS + 5 DP PPQ batches were submitted**

Life cycle management – PAC-MP tool

Testing Sites (DS)

- All analytical methods were developed at an analytical Center of expertise before to be transferred to DS and DP release sites
- all analytical methods expected to be fully validated and transferred to both sites (DS&DP) at time of submission/Inspection

Can «re-usable» PAC-MP be submitted with qualification readiness plan for registration of commercial DS testing site ?

Alternative Manufacturing Site

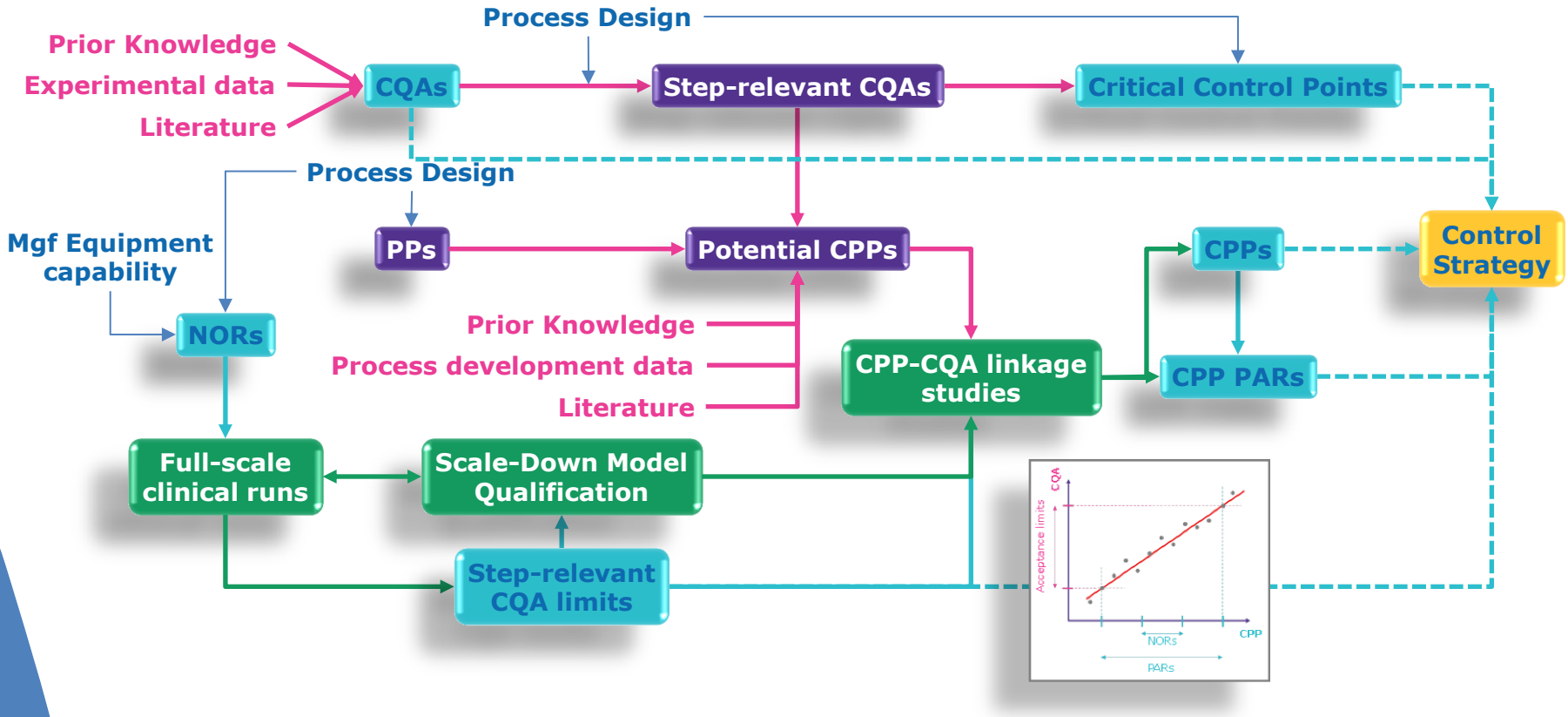
- Although a new process was envisaged with addition of a new manufacturing site, the time to prepare for formal HA interaction and the level of prior knowledge and data was considered premature to introduce a PAC-MP

What is the «suitable» level of prior knowledge and similarity needed to accelerate transfer to a new manufacturing site and foster early discussion with HAs/Inspection ?

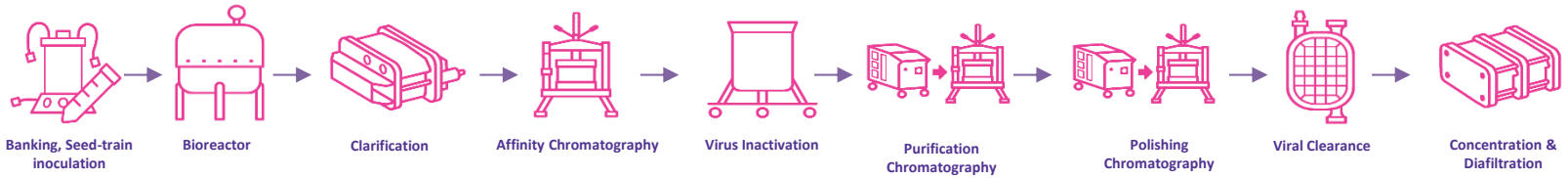
Possibility to use PAC-MP as valuable tool to accelerate original submission or anticipate/down grade change implementation

Back-up Slides

Prior knowledge used for identification of CQAs and CPPs



CPPs could be derived from accumulated knowledge



e.g. Cation exchange chromatography in bind-elute mode

Process Parameters

- Bed height
- Temperature
- Flow rate
- Pressure
- pH
- Conductivity
- Volumes
- Load
- Collection criteria

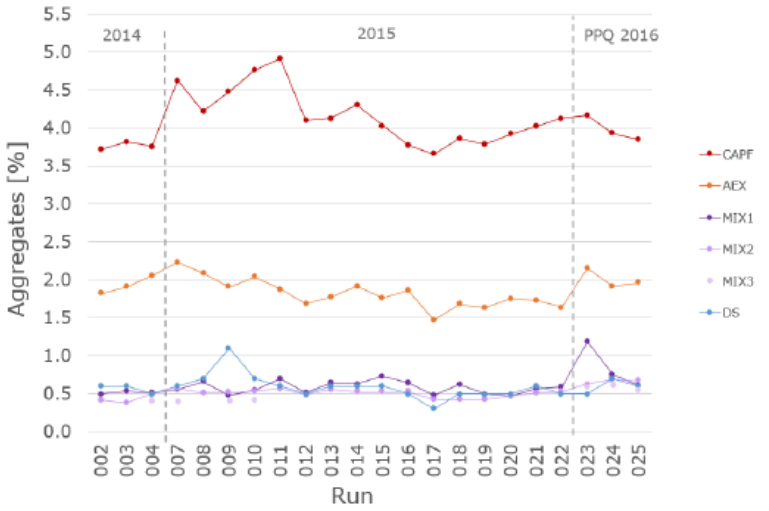
Critical Process Parameters

- Bed height (within non-criticality range)
- Temperature (within non-criticality range)
- **Flow rate**
- Pressure (within non-criticality range)
- **pH**
- **Conductivity**
- Volumes (within non-criticality range)
- **Load**
- **Collection criteria**

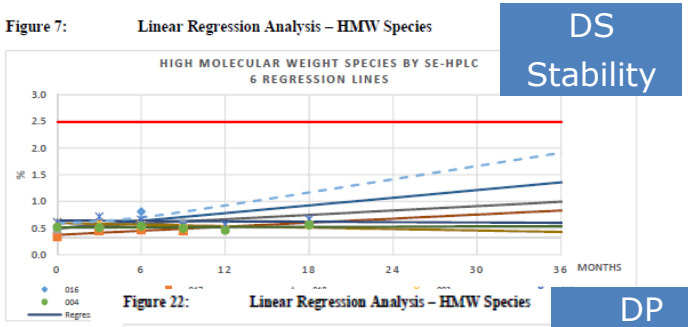
Control Strategy - Example of Aggregates

Prior knowledge

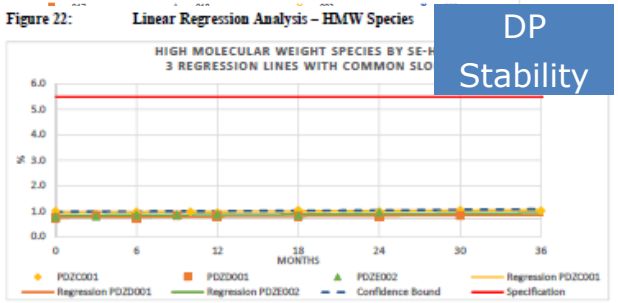
Mabs may aggregate when exposed to low pH and high t°C (not our case) or subsequent to changes of pH for unfolded Mab.



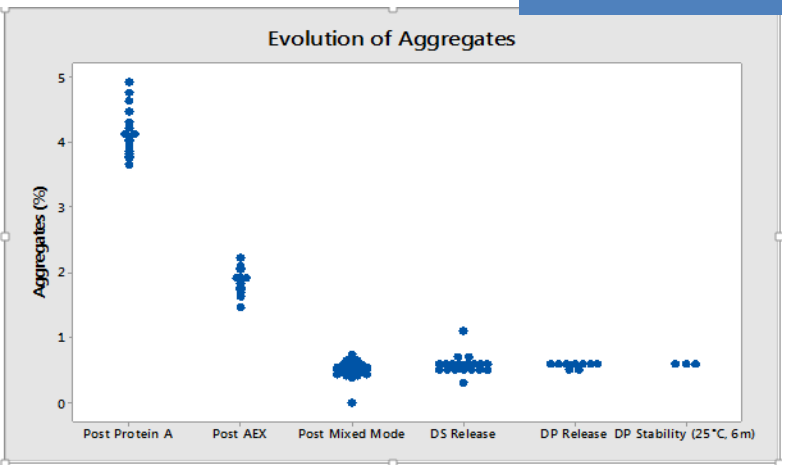
DS Stability



DP Stability



Characterization



Process capability

- **Clinical manufacturing:** Low levels remained consistent across DS batches, subsequent to purification process steps
- **Process characterization and range study:** CPPs with associated PARs are controlled during purification steps (AEX, MM, UF/DF)

Control Strategy

- **CMAs :** Cell culture medium & main feed variability may impact aggregates formation
- **CPPs** Mixed Mode was determined as last step impacting aggregates formation
- **Testing Controls** Initially proposed at DS level only (failsafe) – not a stabilty

Control Strategy - Example of Aggregates

Prior knowledge

Mabs m…
e…
ar…
ou…
sub…
cha…
unfo…

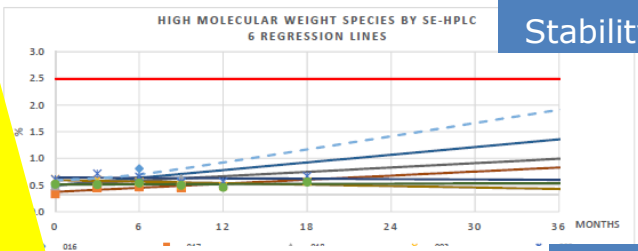
«It may be possible to monitor aggregates as an in-process test with sufficient justification including sufficient PV to support routine use and …evaluation of the effect on product performance and safety including PK and immunogenicity»

Testing was ultimately submitted on DS and DP as failsafe (but not in Stab. S7.2/P8.2) as a minimum control testing was being required in accordance with GMP and Mab Eur Ph. monograph

Could this case be used as prior knowledge if could be demonstrated with a similar molecule ?

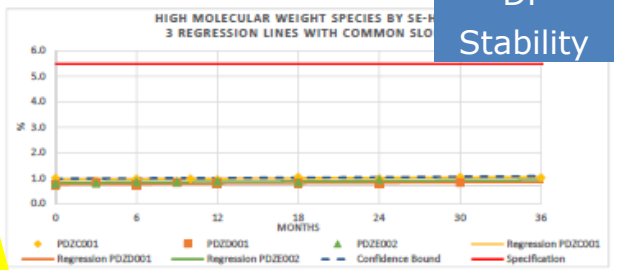
DS Stability

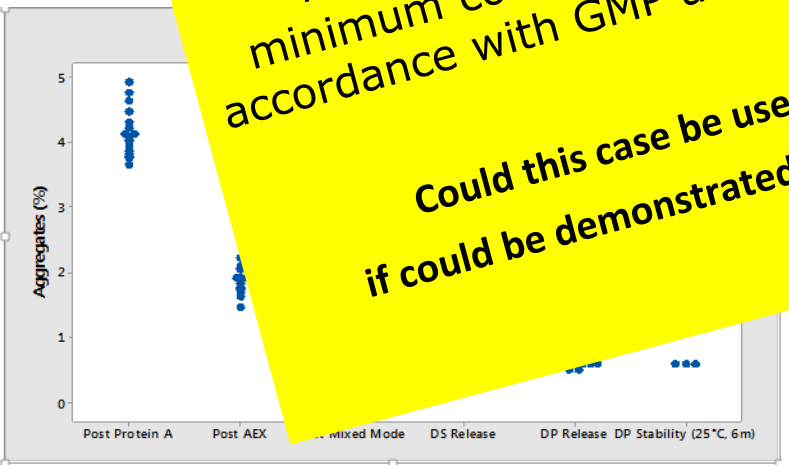
Figure 7: Linear Regression Analysis – HMW Species



DP Stability

Figure 22: Linear Regression Analysis – HMW Species



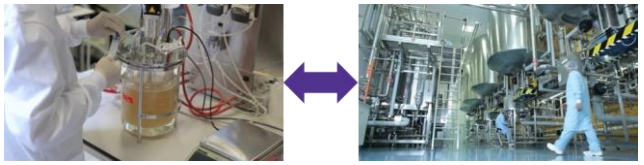


- **Process characterization and range study**:
  CPPs with associated PARs are controlled during purification steps (AEX, MM, UF/DF)

Control Strategy

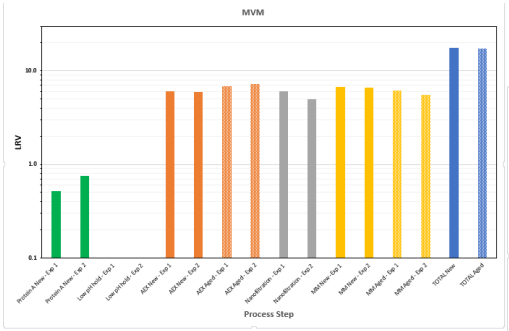
- **CMAs :** Cell culture medium & main feed variability may impact aggregates formation
- **CPPs**
  Mixed Mode was determined as last step impacting aggregates formation
- **Testing Controls**
  Initially proposed at DS level only (failsafe) – not a stabilty indicating parameter

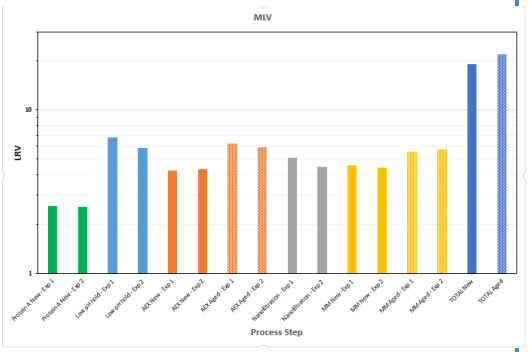
Viral Safety Strategy



1 Viral Clearance Studies

- Spiking experiments and carry over assessment were performed on qualified scale down models to assess viral clearance capacity, on new and aged resins (up to 100 cycles for AEX and MM)
- Cumulative clearance factors were calculated and viral safety risk assessment based on dose provided





2 Resin Life Time Studies

- Small scale resin lifetime studies were completed for AEX and MM resin (up to 100 cycles), and ongoing for Protein A affinity resin.
- Manufacturing scale resin lifetime verification and UF/DF membrane lifetime is being confirmed under concurrent validation protocols.

Viral clearance study on aged resins should be available at time of submission or are requested at D120.

Could prior knowledge (historical data and literature) and impurity clearance capacity over multiple cycles be used to waive some viral clearance study on aged resins?