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

Subteam 4 –

Validation Efficiencies from QbD & Prior Knowledge

Frank Zettl, PhD (Roche), London, Nov. 23, 2017

efpia
European Federation of Pharmaceutical Industries and Associations

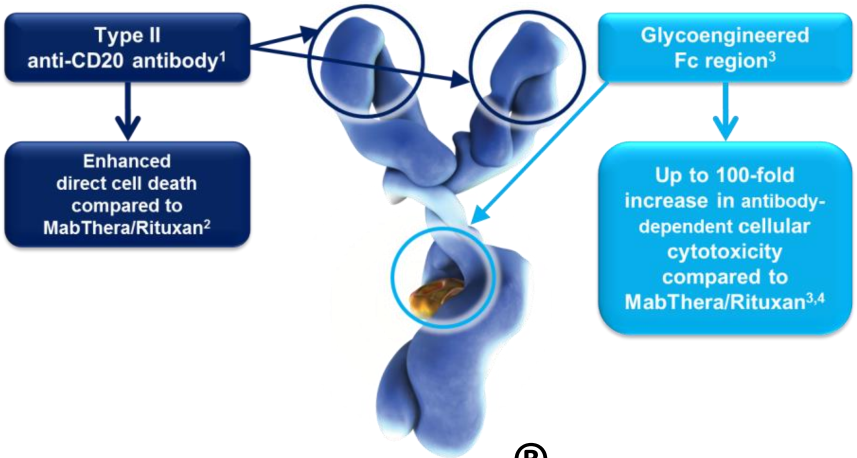
ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

Prior Knowledge Helps to Focus on the Important Topics

- Prior knowledge enables
  - Better understanding of structur/function relationship
  - Design of molecules e.g. to support the mode of action
  - the development/validation of the process



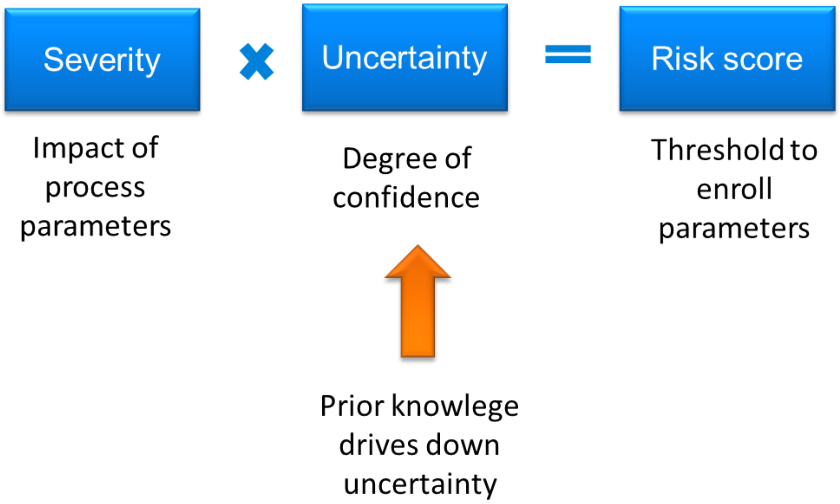
Gazyvaro ®

- Example Gazyvaro®
  - Glycoengineering impacted afucosylation of the MAB (IgG1)
  - Afucosylation increased the ADCC, supporting the mode of action
  - Afucosylation is an important CQA that needs to be controlled in the production process
  - Process validation intensively evaluated most relevant parameters of product and process

Prior Knowledge is Used to Reduce Risk

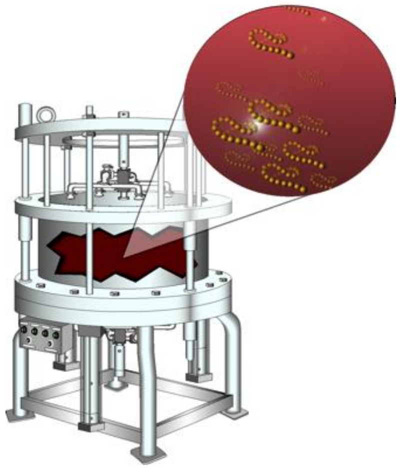
- Not all process parameters can be experimentally evaluated in their combinations even with DoE approaches

- Systematic QbD tools and procedures are implemented for the usage of prior knowledge
- Guide the experimental effort
  - Filtering out pCQAs that don't need to be tested (again)
  - Filtering out parameters that don't need to be studied (again)
  - Filter out studies for unit operations



➔ The selection of process parameters that need to be further studied in more detail is based on prior knowledge

Historical Summary of Protein A Affinity Characterization



- Comparisons between the affinity chromatography steps for eleven monoclonal antibodies were performed
  - Each process was individually optimized to attain highest purity and yield
  - but there are commonalities across many MABs
- Examination of historical affinity process design studies reveals
  - similar low-risk and high-risk parameters (including claimed CPPs)
  - across diverse mAb formats and affinity resins
- A condensation of this prior knowlege is used to support the risk assessment for the design of validation studies

Example: Comparison of Parameter Effects Across Multiple Projects

Impurity A	Parameter													
Molecule	**PP1**	**PP2**	**PP3**	**PP4**	**PP5**	**PP6**	**PP7**	**PP8**	**PP9**	**PP10**	**PP11**	**PP12**	**PP13**	**PP14**
mAb1														
mAb2				-	-									
mAb3		+												
mAb4		+		-		+								
mAb5		+												
mAb6		+		-	-									
mAb7		+												
mAb8		+		-	-									
mAb9		+		-										
mAb10														
mAb11														

Key	
Not studied	Claimed range supported by platform data or no expected impact by parameter or change to process output
Low-Impact	0.33 > IR ≥ 0.10
High-Impact	IR > 0.33
Non-CPP	Minor effect - detectable variation within normal process
Non-CPP	No impact - no detectable variation or response
Worst-case	Parameter performed at known worst-case side based on scientific rationale and development experience
+	Increase observed when parameter performed at upper end range
-	Decrease observed when parameter performed at upper end range

QBD & Evolving Development Strategy – Modelling

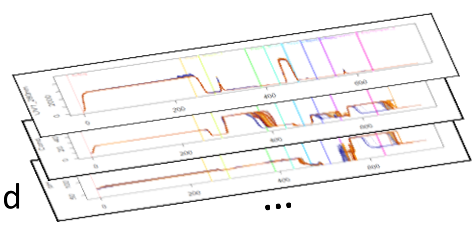
- Machine learning enables an enhanced data driven knowledge management

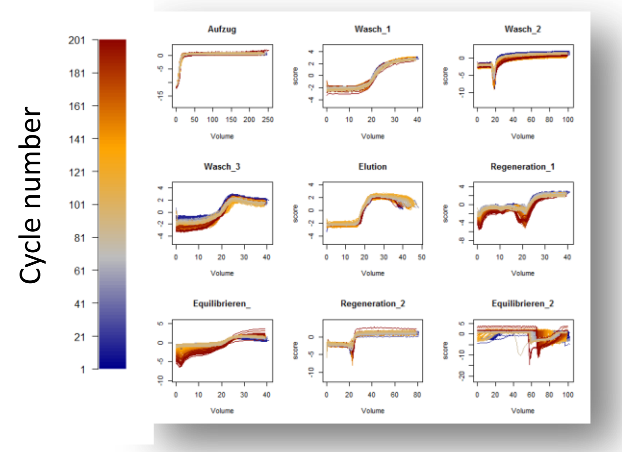
  - Usage of computational models throughout the lifecycle of a product
  - Leveraging automation for knowledge building studies
  - Use available data and mechanistic understanding to create computational models
    - that are applicable to new products
    - support analysis on limited experimental data

  ➔ More product knowledge using less resources

Case Study: Reuse of Affinity Chromatography Resin

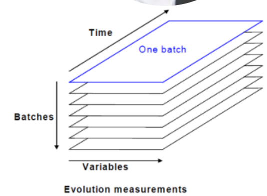
- Resin lifetime studies are very time and feedstock consuming
- They are additionally verified at manufacturing scale
- Platform knowledge shows
    - No impact on a CQAs as a function of resin lifetime
    - Yield might be impacted
- A modelling approach including a series of two PLS (partial least squares) steps is used to predict chromatography performance with regard to yield

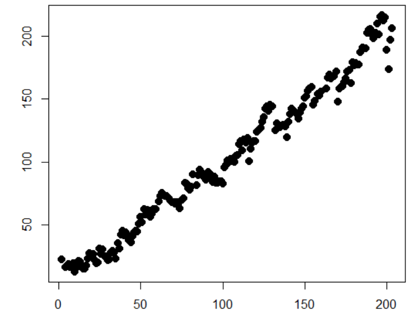




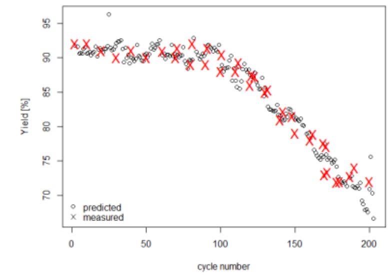
Establishment and application of Column Reuse Model

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

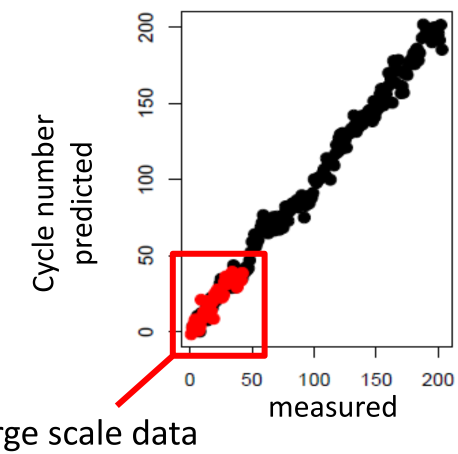




2) Model is trained and extended on small scale MAB A data and large scale Mab B data to predict impact of reuse cycles
-> Patterns across datasets are predictive for impact of reuse cycles on yield



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
- continously improvement with new data from manufacturing