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

Application of Prior Knowledge for Process Parameter Definition

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efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

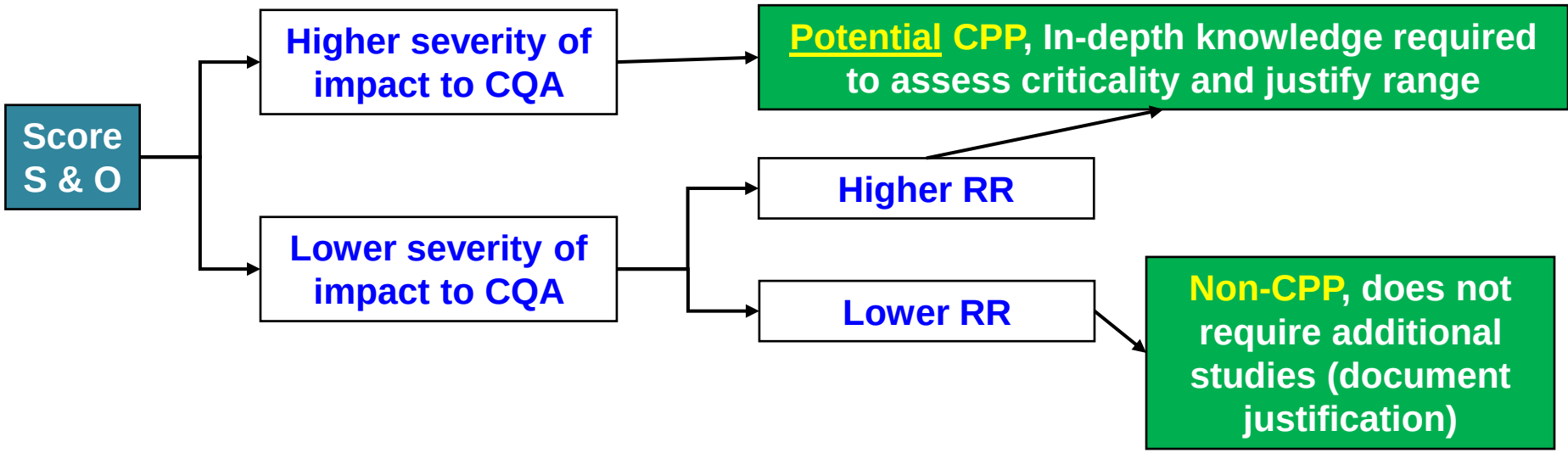
medicines for europe
better access. better health.

Process parameter (PP) definition

- PP definition requires
  - Establishment of acceptable **ranges** in which relevant quality criteria are met
  - Assignment of c**riticality** based on potential to impact CQAs
- For platform processes and unit operations, there can be strong commonality between PPs and their impact
- Effective PP definition requires an effective risk and an inclusive knowledge based framework

Process parameter characterization sorting tool assesses potential criticality, risks and knowledge requirements

- Assess risk related to process excursions for each PP and CQA:
  - **Severity** (S) of the impact of a PP excursion
  - **Occurrence** (O) frequency of an excursion outside acceptable performance
  - **S x O = Relative Risk (RR)**



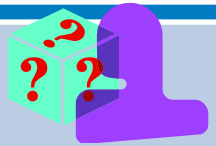
Prior knowledge is an essential input to enable focus on high risk parameters

Prior Knowledge Assessments (PKA's) can be applied to systematically analyze platform process data

Can be view as "experiments", addressing specific question(s)…

Except using historical data as the "laboratory"

PKAs process borrows from the principles used for Systematic Reviews



Frame the Question:
(i.e. “Does unit process parameter X control product quality Y in step Z”?)

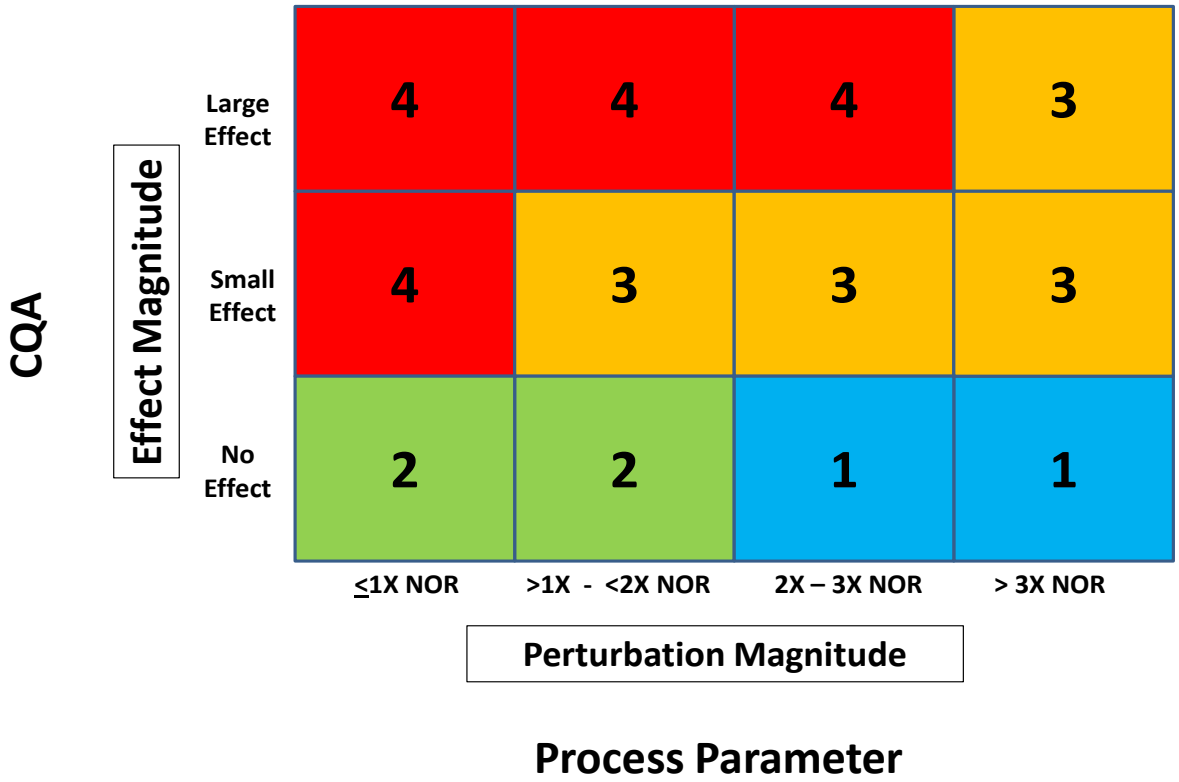
Materials:
Identification of prior knowledge sources
- *Relevance requirements are based on the question*
- *Reliability requirements are based on how the PKA is to be used*

Methods:
Develop processes for data consolidation and analysis.

Review:
Compile and consolidate and analyze information from sources.

Documentation:
Conclusions, recommendations.Does the data meet a burden of proof?

Example - Process Impact Rating (PIR) applied to identify the most impactful operating parameters



Normalizes quantitative impact across products and processes to assess relative impact and importance

James E. Seely, Roger A. Hart, Prior Knowledge Assessments, BioProcess International, 10, 9, 2012

Example - assessment of process parameter impact for chromatography step for one CQA

Report Number	Product	Operating parameter 1	Operating parameter 2	Operating parameter 3	Operating parameter 4	Operating parameter 5	Operating parameter 6	Operating parameter 7	Operating parameter 8	Operating parameter 8	Operating parameter 9	Operating parameter 10	Operating parameter 11	Operating parameter 12	Operating parameter 13	Operating parameter 14	Operating parameter 15	Operating parameter 16	Operating parameter 17
1	A	+	-									+							
2	B	+																+	
3	B												+						
4	C	+										+	+					+	
5	D																		
6	E	+	+																
7	E															-			
8	F	+																	
9	G		-	-															
10	G	+																	
11	H												+						
12	I											+							
13	J												+						
14	K	+																	
15	L	+										+	+						
16	M												+						
17	M																		
18	M											+							
19	M																		
20	M																		

Higher risk operating parameters

James E. Seely, Roger A. Hart, Prior Knowledge Assessments, BioProcess International, 10, 9, 2012

Case study – prior knowledge assessment for cation exchange chromatography for platform MAb process

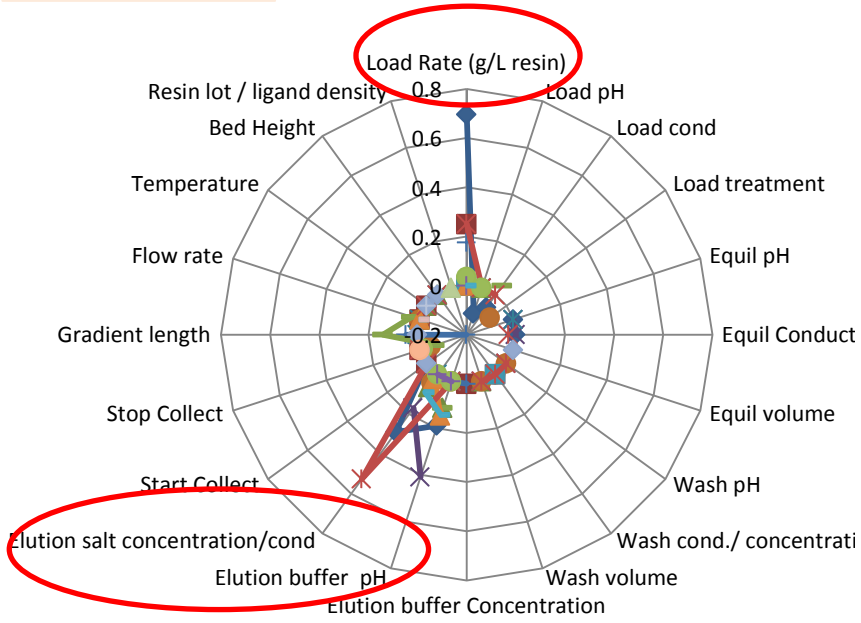
- Chromatography step option for platform MAb processes
- Operated in bind and elute mode
- Primary purpose is clearance of impurities

➢ **Systematically evaluated process design and characterization data from 14 MAb products, as well as extensive manufacturing data.**

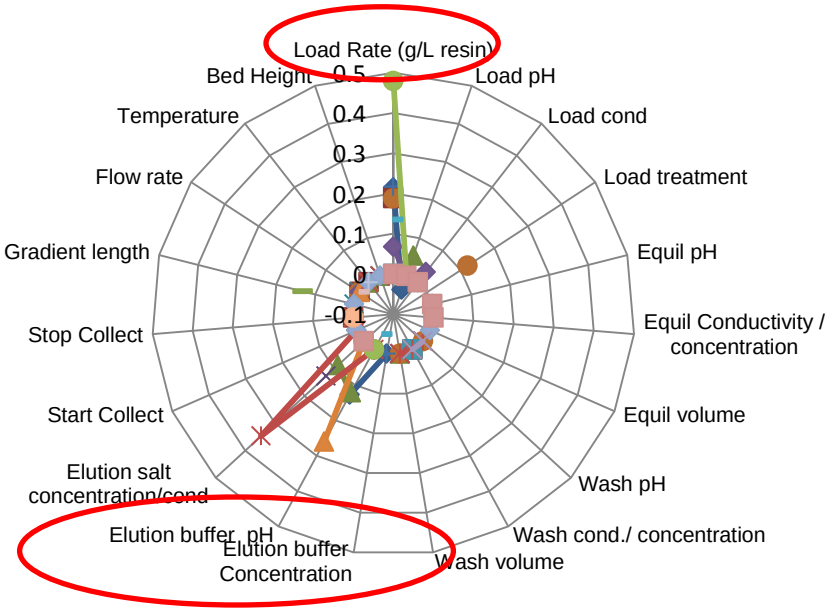
Methodology for this analysis described in *Seely and Hart, Prior knowledge Assessments - Leveraging Platform Process Experience to Develop Targeted Process Characterization Strategies, Bioprocess International, October 2012*

Extensive platform data clearly identify high risk parameters (radial plots of normalized impact)

Impurity 1

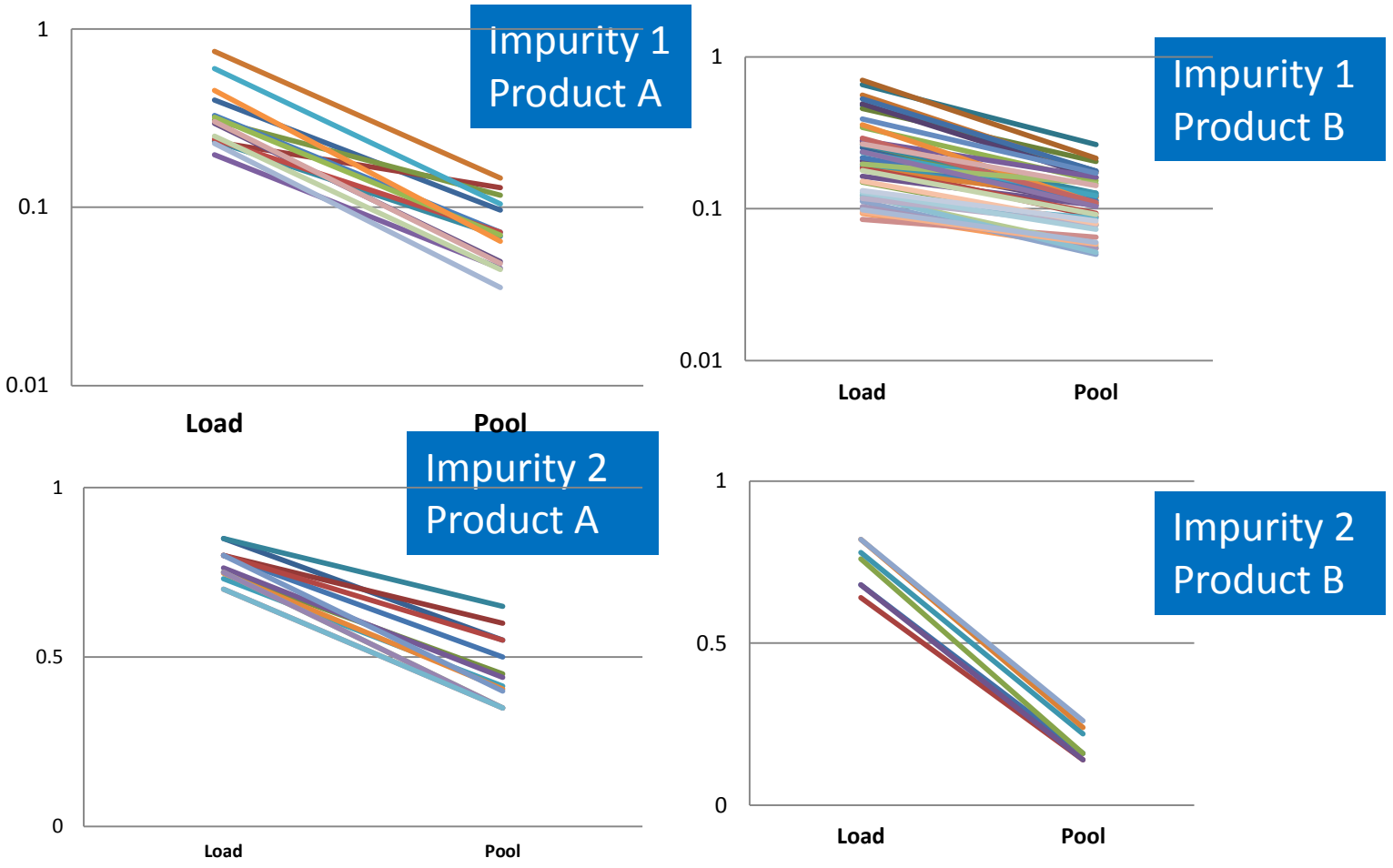


Impurity 2



Same process parameters impact impurities 1 and 2

Extensive manufacturing data across multiple processes indicate the load impurity levels markedly impact impurity 1 and 2 clearance



Example plots – observed for multiple products

Prior knowledge assessment resulted in informed, focused, and effective process characterization

PKA Findings

- High risk parameters clearly identified
- Parameter interactions not practically significant
- No impact of raw materials (including resin)
- Feed stream quality impacts step performance for impurities 1 and 2
- Significant excess clearance capacity for impurities 3 and 4

PC Strategy

- **Focus PC on small number of potential critical parameters**
- **Perform feed challenge/spiking studies to:**
  - **Assess clearance capability**
  - **Establish performance requirements for prior step(s)**
  - **Inform control strategy testing requirements**