Using prior knowledge in process development & manufacturing strategy: The regulator's perspective

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BWP/QWP Stakeholder workshop on prior knowledge

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There are many opportunities for prior knowledge in streamlining process development

- Risk assessments
- Assigning criticality of process parameters
- Justifying the ranges of PARs
- Justifying the omission of some product specific studies e.g. certain resin lifetime studies

There are also may open questions

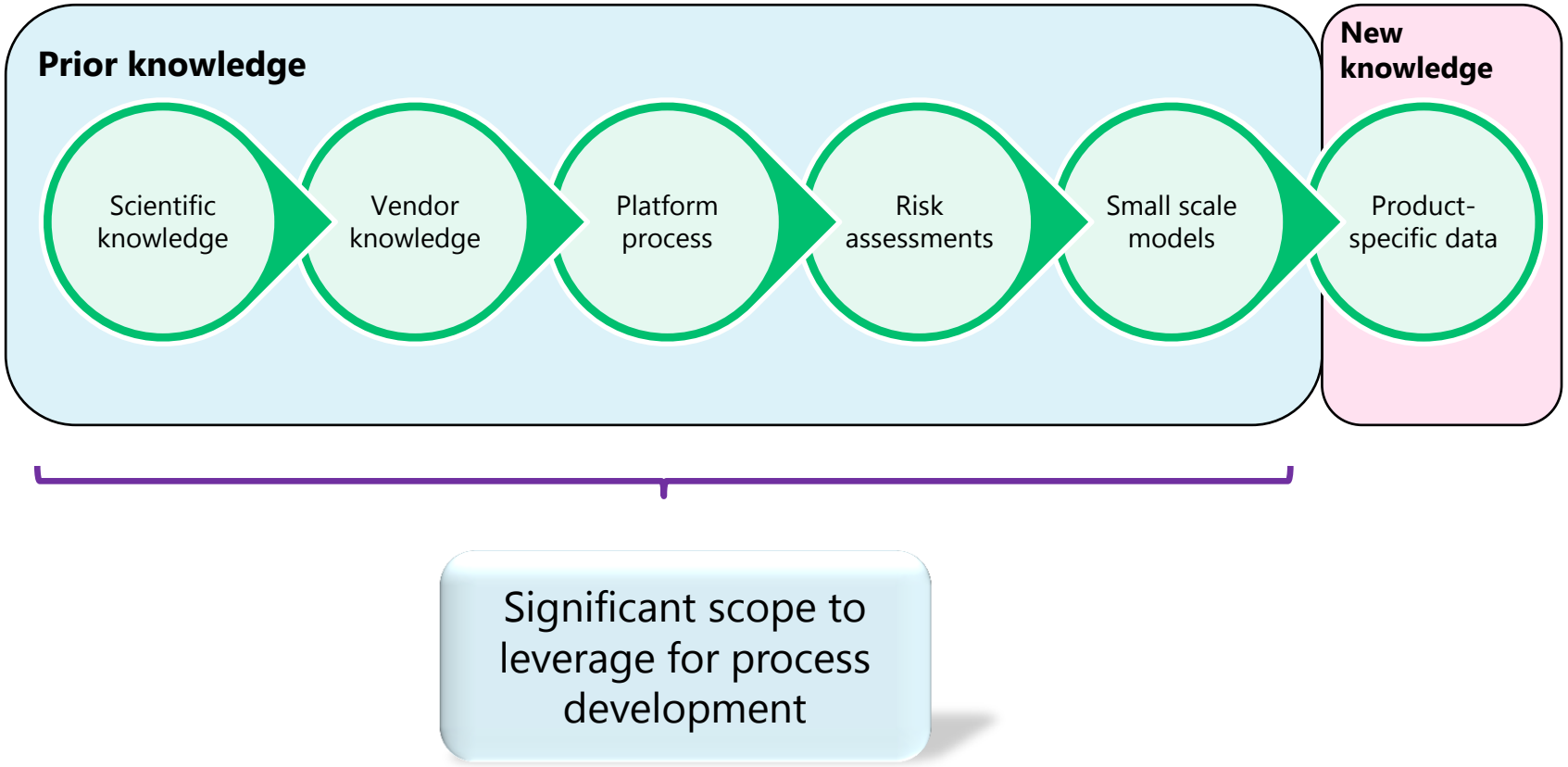
- How can prior knowledge be integrated into process development and control?
- How to balance product-specific data and prior knowledge?
- What to present in the dossier?

For process development we must strike a balance between the need for product-specific data and regulatory flexibility where appropriate

What are the solutions??

- Post-approval validation
- **Prior knowledge**
- Use of models
- PACMPs

Holistic approach


Prior knowledge
Scientific knowledge
Vendor knowledge
Platform process
Risk assessments
Small scale models
New knowledge
Product-specific data
Significant scope to leverage for process development

Prior knowledge represents an untapped area of opportunity

- A vast amount of knowledge can be gained through development of multiple similar products
- If the manufacturing process:
  - Has the same manufacturing steps
  - Uses the same type of equipment
  - Manufactures a “similar” product

…then data from the control of other products could be relevant and can be submitted to the regulators with appropriate justification

Is it reasonable to require risk assessments to be repeated over and over for similar products?

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Theoretical example for chromatography step

Severity		Occurrence				
5	5	6	7	8	9
4	4	5	6	7	8
3	3	4	5	6	7
2	2	3	4	5	6
1	1	2	3	4	5
0	1	2	3	4	5

Process parameter	RPN	Process characterisation
Wash pH	160	Non-CPP
Wash conductivity	160	Non-CPP
Flow rate	140	**CPP**
Load pH	140	Non-CPP
Load conductivity	120	Non-CPP
Resin loading	120	**CPP**
Wash volume	100	Non-CPP
Column bed height	40	Non-CPP
Peak collection stop	40	Non-CPP

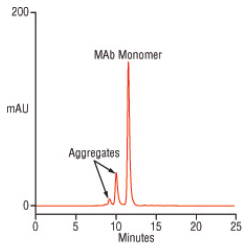
Process characterisation

Low risk – no further study

Could be considered non-CPPs for next product based on prior knowledge

Severity, occurrence and detection may be the same between products

Example: aggregates

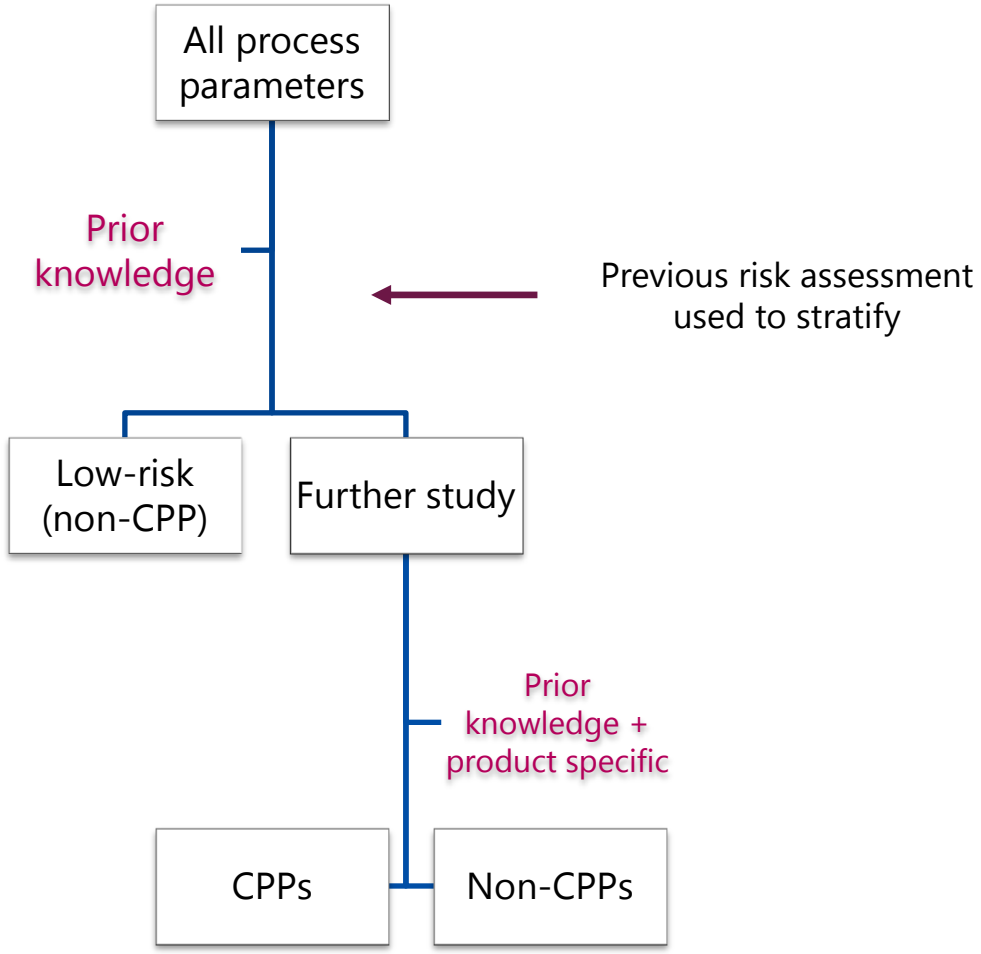


Severity
- Might be considered similar – also depends on patient population, dosing etc.

Occurrence
- Could be slightly different - product specific factors
- Can be factored in to the RPN calculation

Detection
- Same analytical method?

Prior knowledge for defining CPPs



- Studying the same low risk process parameters over and over in repeat submissions of similar products may not be necessary in some cases
- Prior knowledge could allow industry and regulators to focus on those process parameters which are relevant for product quality

The same process parameters can impact the same quality attributes across a product platform

	QA1	QA2	QA3	QA4	QA5	QA6
Process parameter 1	-	+++	++	-	-	+
Process parameter 2	-	+	+	-	-	++
Process parameter 3	-	-	-	-	-	-
Process parameter 4	-	+++	-	-	-	+
QAs to study	X	✓	✓	X	X	✓

Build up knowledge base over multiple products

How might prior knowledge look in the dossier for defining CPPs?

Theoretical example for chromatography step

	mAb1	mAb2	mAb3	mAb4	New mAb
Flow rate	CPP	CPP	CPP	CPP	CPP
Load ratio	non-CPP	non-CPP	non-CPP	non-CPP	non-CPP
Load pH	CPP	non-CPP	CPP	non-CPP	?
Column bed height	CPP	CPP	non-CPP	CPP	?

Prior knowledge

Product specific

Combination of prior knowledge and product-specific data presented in the dossier

Can ranges from previous products be used to justify current ranges?

PARs may change as knowledge accumulates

	mAb1	mAb2	mAb3	mAb4
Buffer pH	6.5-7.5	6.2-7.2	6-8	6-8
Buffer conductivity	25-29	25-29	23-27	20-30
Load ratio	3.0-4.0	3.0-4.0	3.0-4.0	3.0-4.0

Inputs

Outputs
SEC, cIEX, yield, HCP, DNA ....

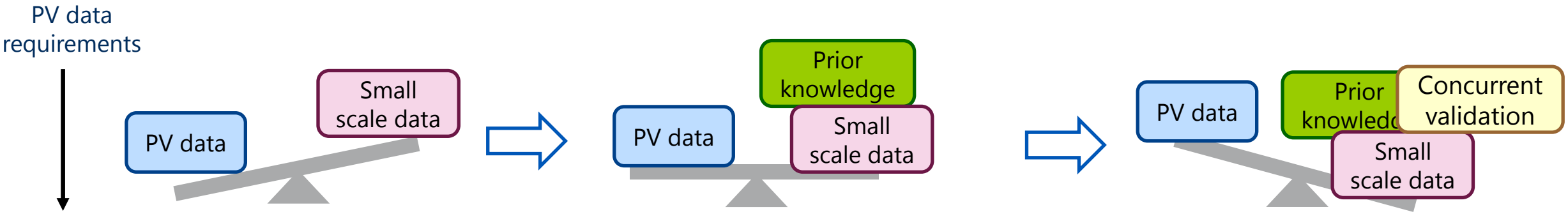
Prior knowledge could be from previous:

- Small scale studies
- Process validation data
- Ongoing process verification

- For each combination of PARs (inputs) there are known outputs (small scale/PV/IPCs) which may be consistent across products
- Models can be developed for each unit operation to show that the proposed operating ranges will always result in a product of acceptable quality based on prior knowledge
- For CPPs, this could be confirmed with product specific small scale studies
- For this type of approach, recommend first getting scientific advice

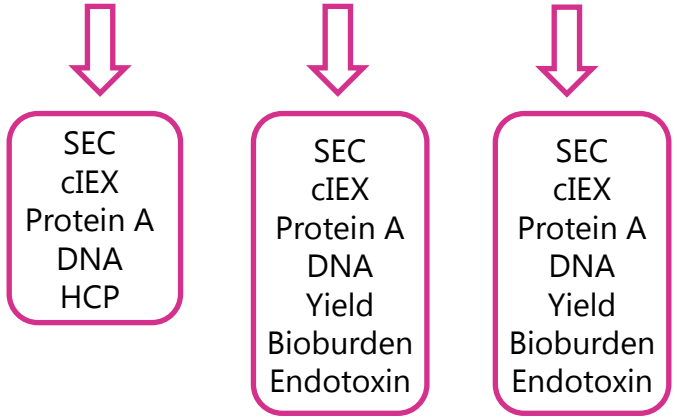
Combining product-specific small scale studies with prior knowledge

- Additional data from prior knowledge could complement some gaps in process validation data or small scale studies
- Combining data from both is particularly useful for products in accelerated development programmes



PARs for each step could possibly be supported by a combination of small scale, full scale and prior knowledge

Edge of range studies	Small scale	Full scale (PV)	Prior knowledge
Flow rate	✓	✓	✓
Load ratio	✓	✓	
Load conductivity	✓		✓
Peak collection start/stop			✓
Column bed height			✓



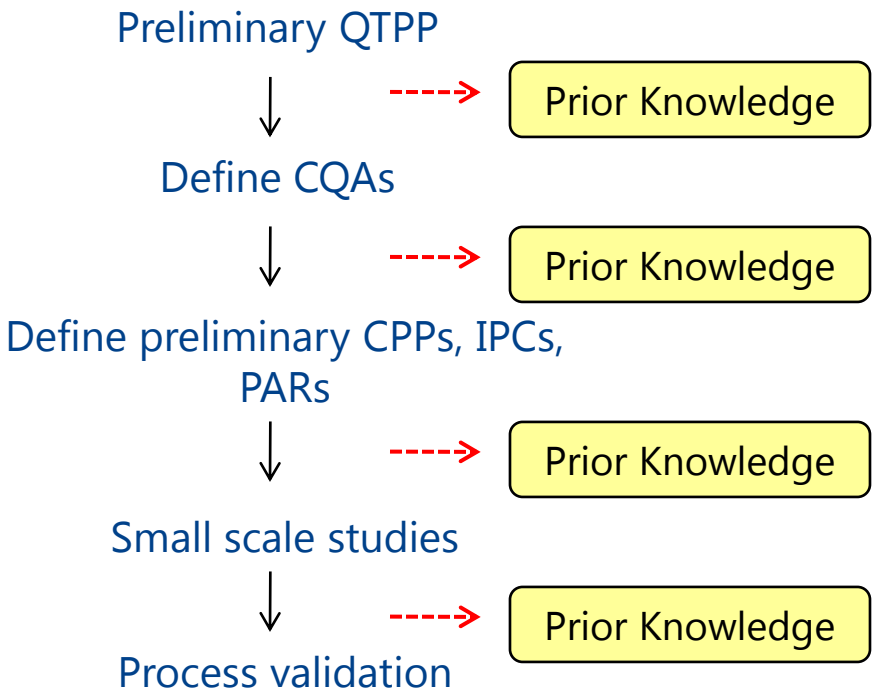
"Enhanced" IPC programme

	Traditional dossier	Accelerated
Bioburden	✓	✓
Endotoxin	✓	✓
Yield	✓	✓
Aggregates		✓
Protein A		✓
HCP		✓
Charge		✓

Filling with a more "restrictive" control strategy

- File with an increased number of IPCs, process parameters and release tests
- Outline in a PACMP the strategy for removal of some of these additional tests post-approval
- Particularly relevant for accelerated approvals

Where can prior knowledge be used during process development?



What to document in the file?

Explain how prior knowledge was used in:

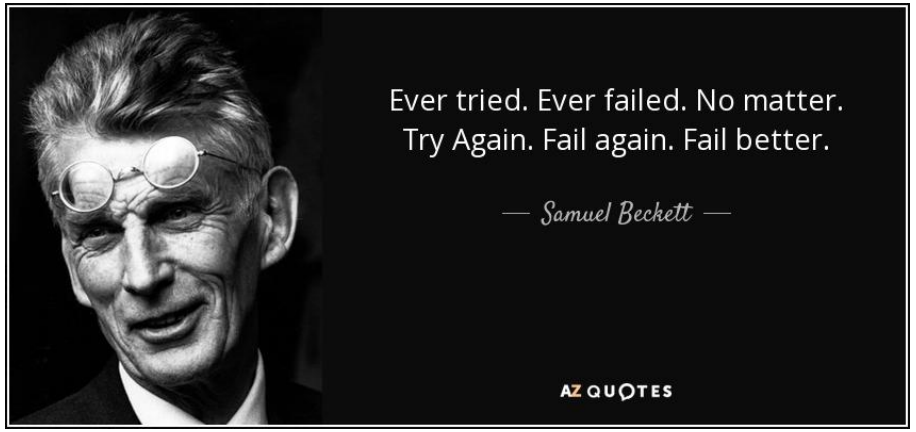
- **Defining the CQAs** … similarity with other products
- **Defining the CPPs** … risk assessments & small scale studies applicable across products?
- **Small scale models** … how is prior knowledge used to decide outputs to study - if manufacturing steps are the same across products then assessment of models could be transferable – same step impacts the same QAs
- **Setting the outer boundaries** of the process ranges .. clearly describe what is prior knowledge and what is product specific

What to present in the dossier

- Where does the prior knowledge come from e.g. other approved products
- Explain and justify how it is relevant for the product
- What are you trying to show with prior knowledge i.e. what product-specific data is it replacing?
- Discuss any remaining uncertainties arising from the use of prior knowledge in place of product specific data (particularly relevant for accelerated development)
- How will such uncertainties will be addressed e.g. use of protocols to agree on further data to be gathered after approval

Final thoughts….

- A holistic approach to process development which uses prior knowledge in combination with small scale models, process validation (concurrent or ongoing process verification) and PACMPs could integrate prior knowledge into product development
- Scope to use prior knowledge in risk assessment, assigning CPPs and setting PARs
- **Challenge the regulators!** - we encourage submissions using prior knowledge so we can move from theoretical to practical examples … use scientific advice
- Using prior knowledge will require clear explanation in the dossier – the easier you make it for assessors, the less questions you'll get!
- Regulators and industry are becoming more closely aligned regarding the possibilities to use prior knowledge …. Many commonalities in 3 upcoming case studies



General considerations from industry

- Ron Ogilvie (Pfizer)

3 case studies

- Bob Kuhn (Amgen)
  - Using prior knowledge in defining process parameters
- Frank Zettl (Roche)
  - Prior knowledge and process validation
- Marie Murphy (Eli Lilly) & Nancy Cauwenberghs (MSD)
  - Prior knowledge in viral safety and resin lifetime studies