HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Process validation and accelerated access – challenges and solutions

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Challenges

- How do you speed up process validation activities in line with a shorted clinical development programme?
- Unfortunately there's no single easy solution

"If it were easy everyone would do it!"

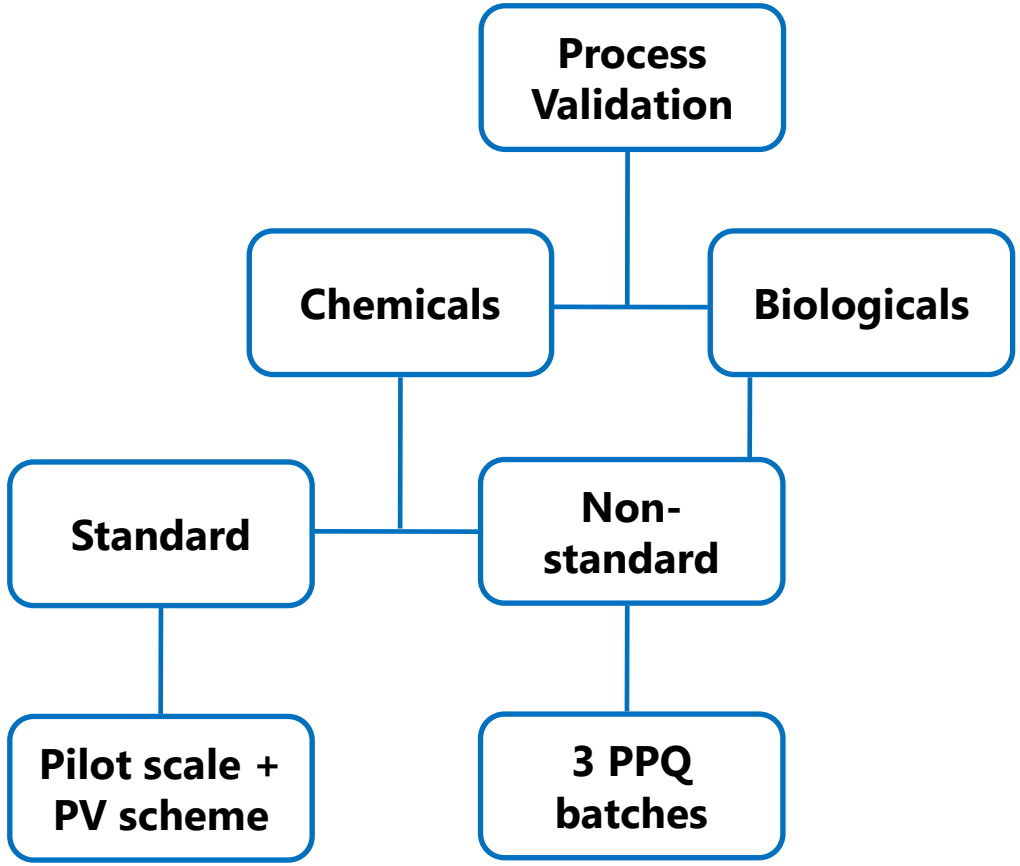
What are the solutions?

- Innovative control strategies
- Use of models
- Prior knowledge
- Tailored process validation packages
- PACMPs

Holistic approach

Accelerated development programmes must balance regulatory flexibility with having an **appropriate level** of process validation data available at the time of approval

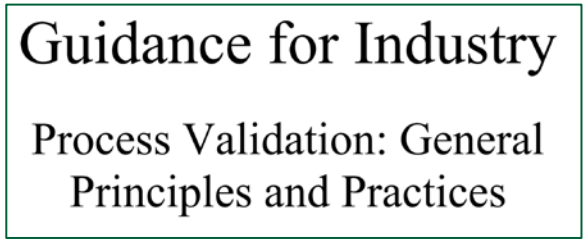
Current process validation requirements



- In Europe, for chemical products which use "standard" methods of manufacture, process validation data from the commercial scale process is not required to be included in the dossier
- A process validation scheme can be submitted instead (data available on inspection)
- Non-standard manufacture (which includes biologicals) require PV data pre-approval.
- However, it is possible for the applicant to justify that the process can be considered standard for a particular manufacturer / site taking into account the risk to the patient of failure of the product or process.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf

Available tools



Process Validation

- **Process qualification/ verification**
  - "Traditional approach"
  - Based on 3 PPQ batches
- **Concurrent validation**
  - PV conducted in parallel with routine production
  - Possible when there is a strong benefit/risk
- **Continued/on going process verification**
  - Post-approval demonstration that process remains in a state of control during routine manufacture
  - Uses trending and statistical process control
- **Continuous process verification**
  - In-line/on-line /at-line controls
  - Requires high level of process understanding
  - PAT and multivariate statistical process control

Ongoing/continued process verification protocols

- Protocols routinely used for e.g. full scale validation of resin lifetime and validation of re-filtration but in general are relatively under- utilised
- A more targeted use of protocols could facilitate **deferral** of certain process validation data to post-approval phase
- They could provide assurance to regulators that the appropriate data will be gathered and evaluated post-approval
- Could cover the entire manufacturing process or individual steps
- Where the license will need to be varied post-approval, a PACMP is more appropriate e.g. relaxing the control strategy after filling with additional controls and narrower ranges

What should be included in a protocol?

- ✓ What will be measured?
- ✓ How will it be evaluated?
- ✓ What are the acceptance criteria?
- ✓ Details of trending and statistical process control
- ✓ How will data be communicated?

"Tailored" validation package

- EMA and FDA guidelines state that concurrent validation can be used in exceptional circumstances, where there is significant patient benefit or limited demand e.g. orphan drugs (GMP Annex 15)
- However, concurrent validation is not an all or nothing approach. A mix of PPQ and concurrent batches could be considered e.g. 1-2 PPQ batches in MAA/BLA plus 1-2 batches validated concurrently
- The strategy for concurrent validation could be supported by a protocol
- This approach has already been accepted in principle by EMA
- This might allow applicants to defer submission of some validation data to post-approval phase, depending on benefit/risk profile

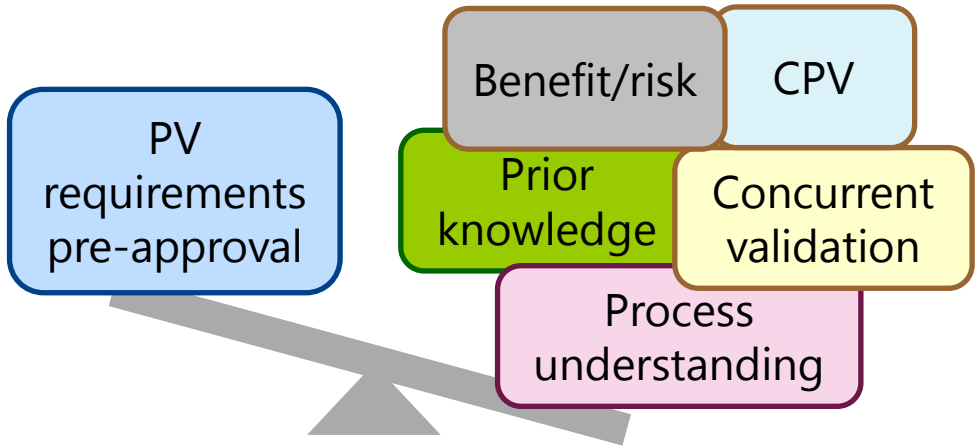
"Tailored" validation package drug product example

Manufacturing step	Risk
DS thaw	
Pooling	
Excipient buffer prep	
Mixing	
Sterile filtration	
Filling	
Lyophilisation	
PFS/AI assembly	
Compatibility	

High
Medium
Low

- The level of process validation data required pre-approval could be linked to the risk associated with the manufacturing step
- May be possible to provide a mix of pre-approval PV data complemented by **prior knowledge** and a **protocol**
- Certain process steps, e.g. sterile filtration, are considered higher risk and will require more validation data pre-approval

Conclusions



- ✓ There is no one-size-fits-all solution
- ✓ A combination of process validation approaches may be necessary to avoid delayed submission/ approval for products on an accelerated path
- ✓ Be clear and transparent regarding deferred data and provide a plan to acquire data post-approval (with proposed timelines)
- ✓ Communication with regulators is critical!
- ✓ Consider a holistic approach by using protocols, concurrent validation, risk assessment, prior knowledge, process understanding and benefit/risk assessment to justify any deferral of process validation data