

# Using Prior Knowledge and accelerated CMC tools to support early access to medicines

Seán Barry  
Senior Pharmaceutical Assessor  
HPRA, Ireland

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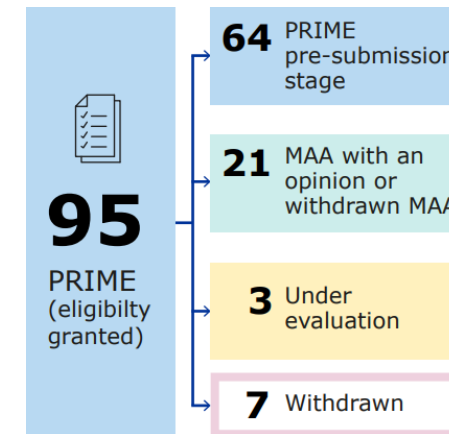
## Early access and accelerated CMC

- Many regulatory agencies have developed specific pathways for promising products treating unmet medical conditions e.g. Priority Review, PRIME, Breakthrough, Sakigake
- Recent years have seen an increase in critical medicines entering such early access programmes



- Often, this may be on the basis of early promising clinical data, e.g. phase 2 data, with confirmatory clinical studies completed post-approval
- This new paradigm means that CMC development timelines are compressed
- At the time of filing, the full CMC package may not yet be available
- Accelerated CMC tools can facilitate earlier approval with additional CMC information gathered post-approval

Overview of eligible PRIME products and MAA status (to June 2021)





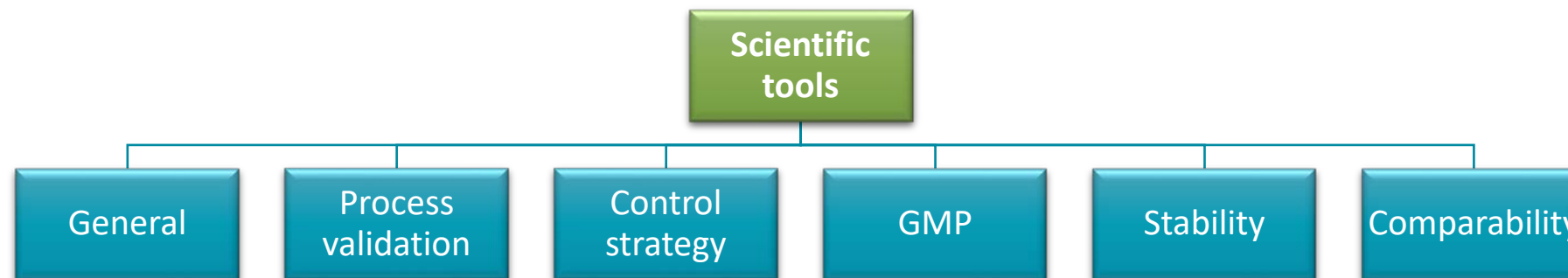
# EMA Toolbox guidance



22 April 2022  
EMA/CHMP/BWP/QWP/IWG/694114/2019  
Committee for Human Medicinal Products (CHMP)

Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

- The EMA Toolbox guidance was developed to amalgamate the various regulatory flexibilities currently available
- It describes various scientific and regulatory tools which can be used to accelerate CMC
- These tools are currently applicable to products with PRIME designation or products to treat an unmet medical need





## Validation tools - Concurrent validation

- Process validation may not be complete at the time of approval
- Concurrent validation allows formal validation to be completed post-approval based on a protocol, which should include:
  - Scope of validation activities
  - Tests (release testing, process parameters and IPCs)
  - Justification for the validation acceptance criteria
  - Supportive data can be provided from other non-PPQ batches
- Data can be provided post-approval through various mechanisms in the EU system e.g. Specific Obligation, Recommendation
- Regulatory approval is generally not required for release of concurrent validation batches to the market



## Control strategy tools

- In order to facilitate faster access for patients, some process development and evaluation studies could be deferred to post-approval
- Applicants could file with an **adapted control strategy** to offset the reduced level of knowledge, could encompass some or all of the following elements:
  - Additional specifications
  - Additional IPCs
  - Additional process parameters
  - A higher number of CPPs
  - Narrower ranges for CPPs
- Data can be provided post-approval to support removing/widening of controls, this could be agreed up front in a PACMP



## Specifications

What to do when there are few batches produced with a limited number used in clinical trials ?

- Available batch data at time of MA may not capture the normal manufacturing variability
- High risk of OOS results if specifications are set based on limited numbers of batches
- It is possible to agree acceptance criteria which are wider than available batch data and wider than the levels used in clinical trials
- However, there needs to be a proper justification (i.e. not high level or vague) that the limits will result in safe and efficacious batches. Use all available data for such justifications, e.g.
  - Prior knowledge
  - In vitro data
  - Data from dose finding studies
- Agreement at time of MA approval on how the limits will be evaluated and revised if necessary (e.g. through a PACMP with agreed timepoints)



SPECIFICATIONS



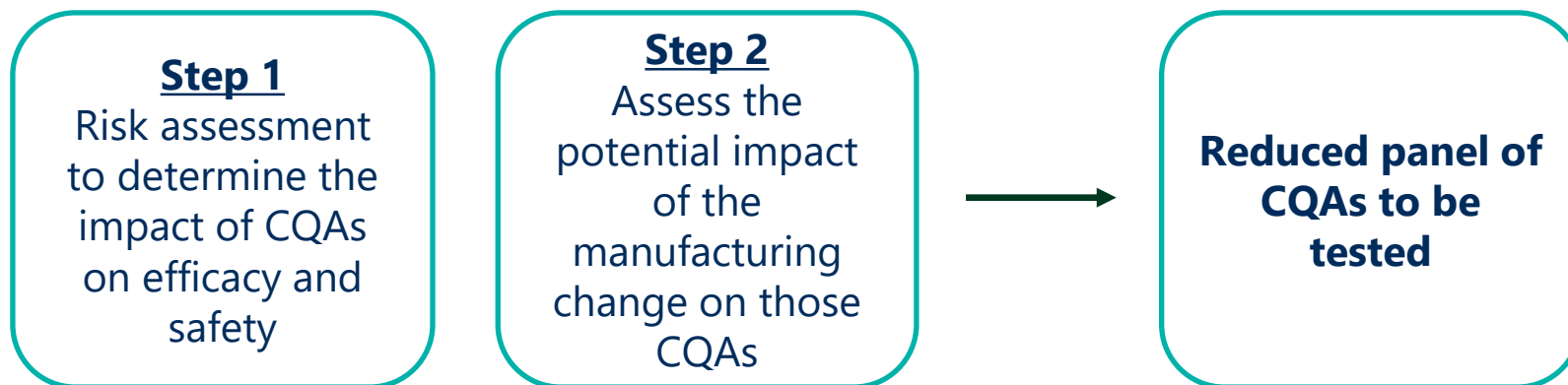
## Stability tools - biological

- Toolbox allows for shelf life extrapolation using predictive stability models generated from prior knowledge of structurally similar molecules.
- May be possible to approve a shelf life which is longer than the available product-specific real time stability data.
- Important to show that the current product fits the model generated using data from other products
- It may be possible to leverage data from other presentations when establishing the shelf life e.g. vial & PFS
- Need agreement up front what actions will be taken in case the real time stability results no longer fit the model.



## Scientific tools related to comparability (biologicals)

Risk based approaches can be used to reduced the number of CQAs tested in comparability studies → supported by Prior Knowledge

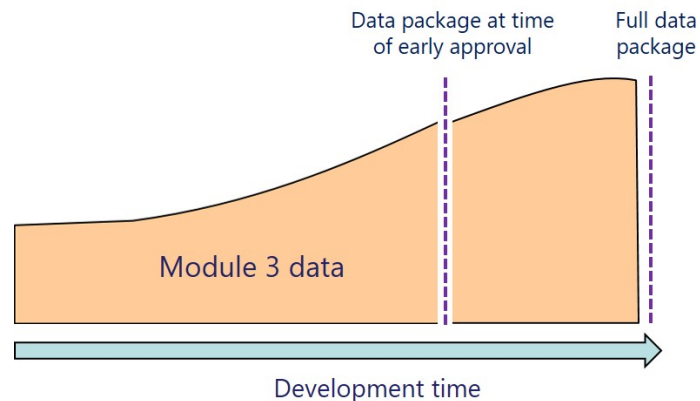


- Consider: Type of change and Analytical capabilities, other data (e.g., small-scale)
- Separate assessment of individual changes could be acceptable
- Separate assessment of part of the process could be acceptable



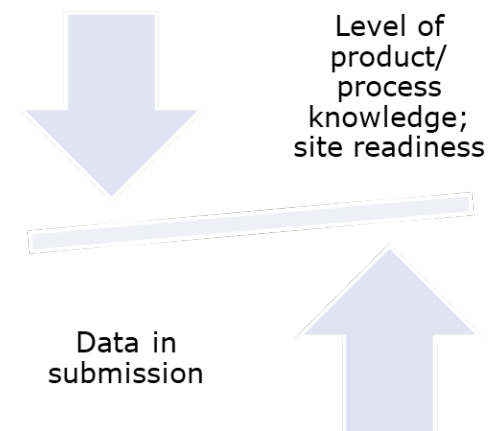


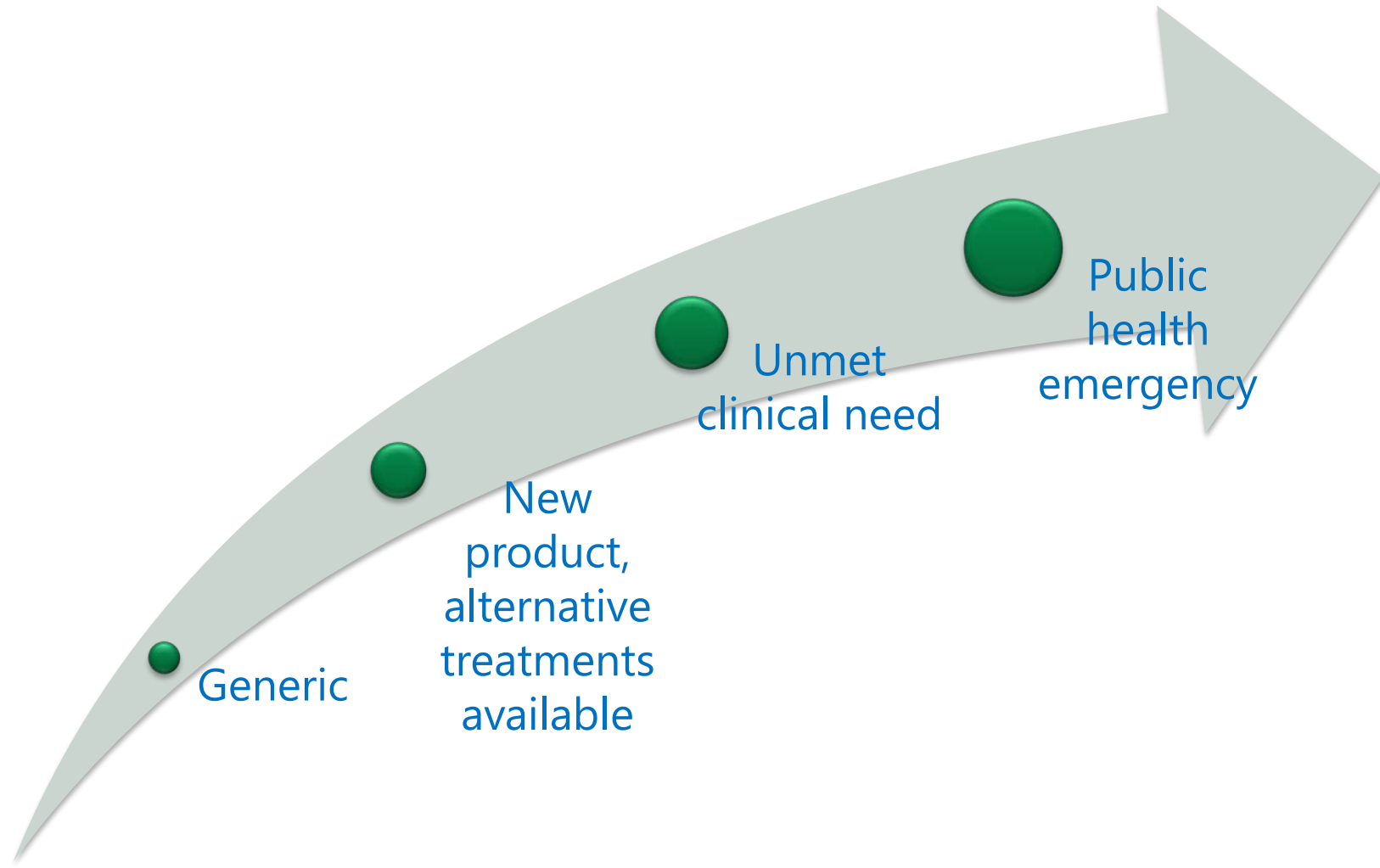
Regulatory flexibilities and early approval do not represent a reduction in standards  
→ rather the **timing of data submission is changed**



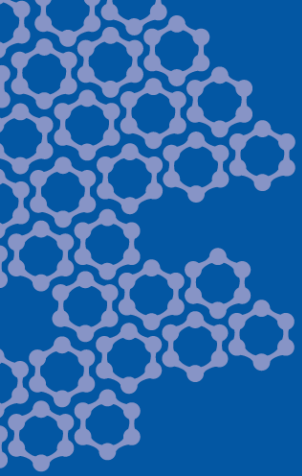
The more process knowledge demonstrated → the higher the flexibility in data requirements

- Regulatory flexibility requires an appropriate supporting data package
- Uncertainties and risks due to incomplete data at time of approval need to be appropriately mitigated by e.g.:
  - Demonstrated manufacturing experience
  - Prior knowledge
  - Sufficient characterisation
  - Demonstrated product understanding
  - Appropriate control strategy





Level of regulatory flexibility



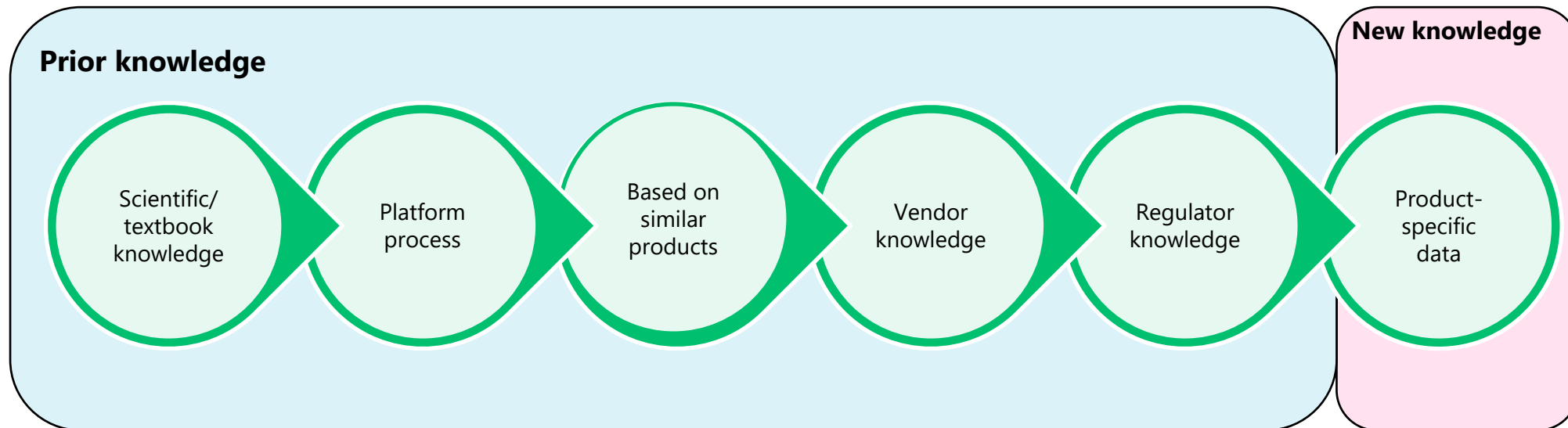
# Prior Knowledge

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## What is prior knowledge?

- ▶ Established term which is used in ICH Q8, Q10 & Q11





## What can prior knowledge be used for?

- To guide development and formulation
- Underpin the control strategy
- Risk assessment and criticality assignment
- Supplement process validation data
- Justify ranges of process parameters and specifications
- Justify shelf life
- Avoid re-assessment of dossier sections
- Accelerate the start clinical trials
- Life cycle management





## Prior knowledge

Prior knowledge of quality attributes and processes can be used to support control strategy flexibility, including acceptance criteria and process parameter ranges outside of manufacturing and clinical experience.

- Needs to be shown **to be applicable** for product in question.
- Include data in MAA file where it replaces product specific data
- Could allow postponement of certain studies to post approval or replace product specific data.
- Platform approach: provide information on qualification of the new product to the platform
- Also applicable to assay qualification



## Prior knowledge example (chromatography step for mAb manufacture)

	mAb 1	mAb 2	mAb 3	mAb 4	mAb 5	mAb 6	mAb 7	mAb 8
Column bed height								
Load flow rate								
Load capacity/ratio								
Load pH								
Load conductivity								
Wash buffer volume								
Wash flow rate								
Wash pH								
Wash conductivity								
Elution buffer volume								
Elution flow rate								
Elution buffer pH								
Elution conductivity								

\*Green shading indicates where a process parameter was studied in DOE

- The Applicant had performed numerous DoE process characterisation studies for this manufacturing step for similar mAb products
- The names of all the products were provided
- It was clearly indicated which process parameters were studied for which product
- A statistical model was used to justify which process parameters are critical for the platform
- The ranges were justified based on the platform
- No product specific process characterisation studies were required for this manufacturing step



## How to refer to prior knowledge in the dossier

- Explain where the prior knowledge comes from and how it is relevant for the current product ... **it's all about context!**
- Discuss any remaining uncertainties arising from the use of prior knowledge in place of product specific data
- How will such uncertainties be addressed e.g. use of protocols to agree on further data to be gathered after approval
- Remember in the end it's always linked to the **benefit/risk** ratio





# Lessons from the Covid-19 pandemic

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# Regulatory flexibilities used to support approval of Covid products

## Scientific tools

- Alternative process validation approaches
  - Concurrent validation
  - Decoupling DS & DP PPQ
- Prior knowledge/Platform
- Predicted shelf life
- Comparability protocols
- Interim specifications
- Submission of data post-approval

## Regulatory tools/work practices

- Rolling reviews
- Emergency authorisations
- Conditional authorisations
- Continuous communication
- Remote inspections
- Sharing of inspection reports
- PACMPs



# Examples of flexibilities from recent EPARs

- Covid-19 Vaccine Janssen
  - Based on experience with the **Ad26 vaccine platform** products, CQAs, CMAs and CPP have been assigned
  - A process control strategy was developed based on extensive **AdVac/PER.C6 platform experience** ...
  - The shelf life is based on **platform data** from similar Ad26 products
  - Comparability data is requested for the second finished product site **to confirm the FP is comparable** to the FP from the first commercial site and the clinical material
- Vaxzevria
  - Validation has not been completed. **Validation protocols** are provided.
  - **Completion of the comparability data package** is still requested and further data are requested after approval
- Ronapreve
  - The proposed shelf life .....is based on product-specific data, in conjunction with the Applicant's **extensive platform manufacturing experience** and product knowledge, as well as long-term stability data **from other IgG1 antibodies from the Applicant**.
  - A combination of development, **prior knowledge**, clinical manufacturing experience and process validation was used to define the proposed commercial manufacturing process and process controls



## Learnings

- Alternative approaches and flexibilities in data submissions have been used extensively for all authorized COVID vaccines
- Extent of **regulatory flexibilities** subject to **product/process knowledge & site readiness.**
- **Early and transparent interaction** with Regulators highly recommended
- **Distant assessments** useful alternative means of verifying GMP compliance
- For lifecycle management, regulators need a clear prioritisation of changes based on supply impact



## Closing remarks

- Regulators are open to using **appropriate** flexibilities in the interest of patient access when supported by an appropriate benefit/risk
- The new flexibilities outlined in the EMA toolbox have already been used for several PRIME products and for Covid-19 vaccines and therapeutics
- Demonstration of Prior Knowledge forms a key part of accelerating CMC approval
- The pandemic has given renewed impetus to regulatory collaboration and harmonisation
- Global collaboration projects such as the ICMRA collaborative assessment pilot\* may be a starting point for a globally harmonised approach to the use of regulatory tools



3 February 2021  
EMA/73033/2021  
International Affairs

Questions and Answers on the Pilot Project 'OPEN'  
Opening our Procedures at EMA to Non-EU authorities



\* [https://icmra.info/drupal/en/strategicinitatives/pqkms/pq\\_pilots\\_call\\_for\\_industry\\_applications](https://icmra.info/drupal/en/strategicinitatives/pqkms/pq_pilots_call_for_industry_applications)