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Objectives and impact of the draft revision of the EMA PV guidance

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Glossary – Process validation

- **Validation** is the act of demonstrating and documenting that a procedure operates effectively
- **Process validation** is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of consistently producing a finished product of the required quality

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Glossary – Process validation

- Annex 15 to the EU Guide to GMP:
  - Process validation: the documented evidence that the process operated within established parameters can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

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Glossary – Continuous process verification

- **Continuous process verification**: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8)
- **Continued process verification** – the third stage of process validation in the lifecycle of the process after process design and qualification. The goal is to continuously assure that the process remains in a state of control (the validated state) during commercial manufacture (draft FDA guidance on process validation)

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Validation: Not a once-off event

- Validation should not be viewed as a once-off event
  - Has never been a once-off event
- A lifecycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routing commercial production.

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Update of note for guidance on process validation

- **Draft revision published April 2012**
- **End of consultation period Oct 2012**
  - Introduces the possibility to use continuous process verification
  - Biological products being brought into scope
    - Fundamental principles apply, but should be taken on a case by case basis
  - Harmonisation with FDA guidance
  - API covered under ICH Q11
  - Revision of Annex 15 is envisaged accordingly

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf

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Impact of revision on authorised products

- No new requirements on medicinal products already authorised and on the market
- Will clarify how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality management system as described by ICH Q10

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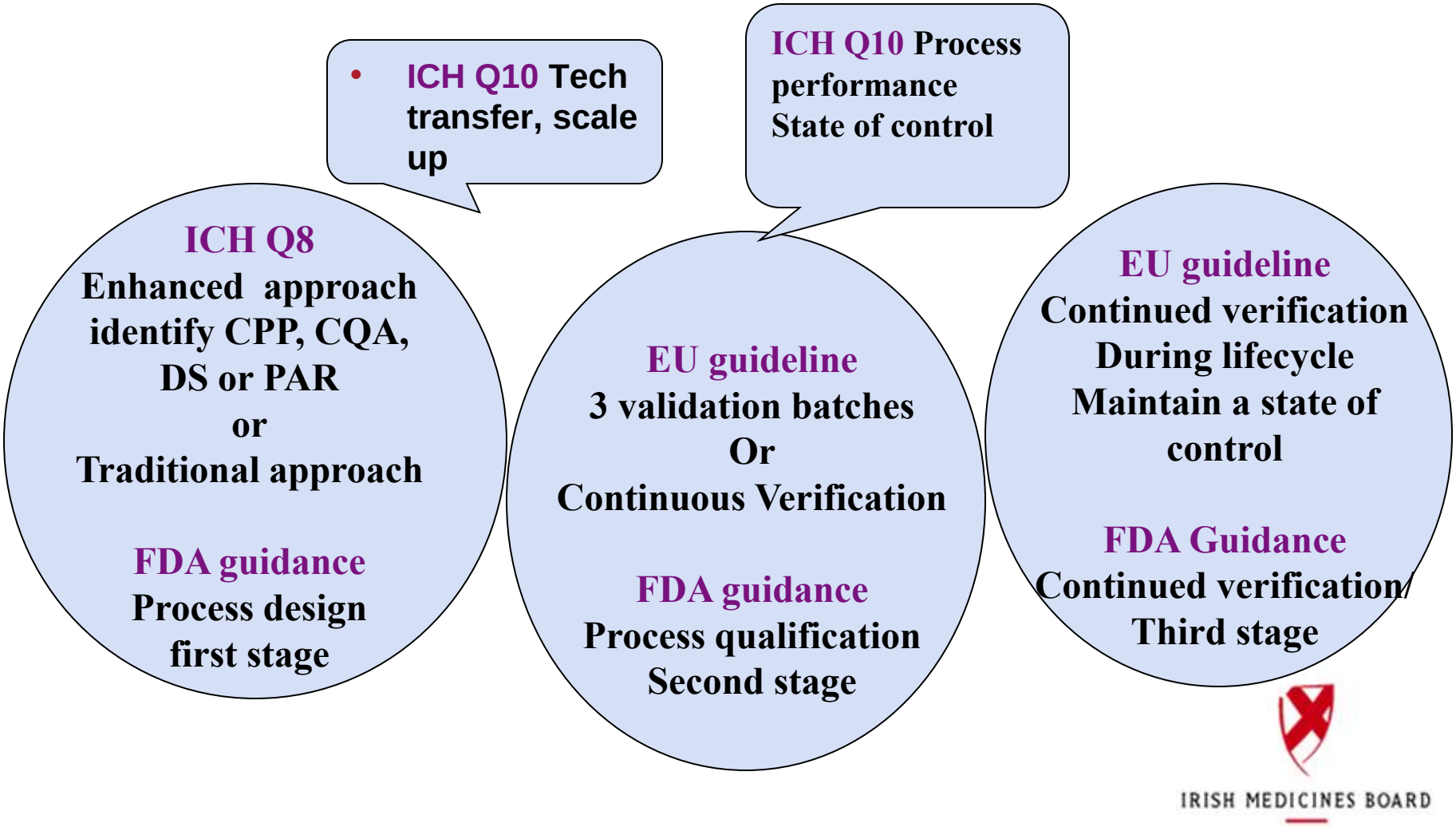
EU vs FDA approach (and ICH Q8-10)



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Differences between FDA and EU guidance

- FDA guidance is manufacturing and activity related
- The EMA guideline provides guidance on the information to be considered for dossier submission
  - Aimed at industry and assessors
  - Annex 15 on GMP to be updated accordingly

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EU approaches to process validation

- Traditional process validation
  - X- number of batches
- Continuous process verification (CPV)
  - May be more suitable for products with continuous processing or enhanced development
- Hybrid approach
  - Mixture of traditional and continuous. Approach should be justified
- **All approaches are acceptable alternatives**

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Traditional process validation

- No major changes to requirements
  - Information on when intended batch size is less than 100,000 units
  - Update to definition of non-standard processes and information to be provided
  - Inclusion of verification of design space

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Continuous process verification

- Extensive in-line or at-line controls should be performed and process performance and product quality monitored in a timely manner.
- Relevant process quality attributes of incoming materials or components, in-process material and finished products should be collected.
- Include the verification of attributes, parameters and end points and assessment of CQA and CPP trends.

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Continuous process verification

- Scope and extent influenced by:
  - Prior development and manufacturing knowledge from similar products / processes
  - Extent of process understanding gained from development studies and commercial manufacturing experience
  - Complexity of the product / manufacturing process
  - Level of process automation and analytical technologies used

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Continuous process verification

- Need systems in place to monitor and adjust the process
- Extent and frequency of sampling and testing are key elements
- The process should be verified on commercial scale batches prior to marketing
- The applicant should define the stage at which the product is considered to be validated and the basis on which the decision was made.

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Advantages of CPV

- Facilitates process improvements
- Adjustment of the process to maintain product quality
- Validation data not required in the dossier for non-standard processes
- Verification of design space at commercial scale not required

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Hybrid approach

- Use of either traditional approach or CPV for different steps within the manufacturing process
- Justification should be provided clarifying which approach has been taken for which step

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Rationale for requesting data in the dossier

- EU GMP inspections are not generally product specific, hence the EU authorities require information on validation with respect to the specific product in the dossier before product approval

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Rationale for requesting data in the dossier

- Traditional approach
  - Standard manufacturing processes considered lower risk and process validation protocol is considered sufficient
  - Non-standard processes are considered higher risk and validation data are required in the dossier

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Rationale for requesting data in the dossier

- Continuous Process Verification
  - Discussion on the appropriateness and feasibility of CPV should be included in the development section of the dossier
    - Including data from at least lab or pilot scale batches

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Rationale for requesting data in the dossier

- A description of the CPV strategy should be included in the process validation scheme as described in Annex 1 with cross reference in the validation section of the dossier
  - Protocols
  - System and equipment for collecting samples
  - Sample sizes

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Rationale for requesting data in the dossier

- In line with GMP requirements protocols reports and SOPs should be available at each concerned manufacturing site along with actual data generated during continuous process verification at commercial scale

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Continued process verification during the product lifecycle

- Product quality should be monitored during commercial manufacture product quality should be monitored to ensure a state of control
- Provide assurance of the continued capability of the process and controls to produce product that meets the desired quality.

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Continued process verification during the product lifecycle

- Process trends should be collected and assessed to verify the validity of the original process validation or to identify required changes to the control strategy.
  - A period of enhanced monitoring and sampling may be of benefit to increase process understanding
  - Discussion on model verification required for high impact models

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Legacy products

- Principles laid down in ICH Q8, Q9 and Q10 are applicable to legacy products
- It is possible to perform a risk assessment and to introduce continuous process verification any time over the lifecycle of the product.
- Legacy products may benefit from historical data and experience gained
- In principle it is never ‘Too Late’

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Continued process verification – frequency of testing

- The extent and frequency of process verification should be reviewed periodically and modified throughout the product lifecycle

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Continued process verification – frequency of testing

- Frequency of sampling and testing in the context of process validation is assessed in view of
  - Criticality of parameter
  - Quality attribute
  - Batch size
  - Equipment
  - Sampling tool
  - Sample size etc…

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Standard vs non-standard processes

- Only for processes which have not been validated using CPV
- Determined by a combination of the nature of the drug substance, the nature of the product, the process itself and the production experience of the manufacturer

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Standard vs non-standard processes

- Some amendments have been made to the following sections
  - Suspensions, emulsions or other liquid dispersed **parenterals**
  - **Modified** release preparations
  - Specialised dosage forms – addition of nanoparticulate preparations
  - Real time release testing and aseptic processing moved to complex processes

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Post approval change control

- GMP change control procedures do not need to be defined in the dossier
  - Refer to the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary products and regulation 1234/2008/EC for details on the changes which would require a variation

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Status of Annex 15 update

- To be updated in light of the revised note for guidance on process validation
  - Concept paper to be drafted

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Use of statistics

- Process capability within and between batches (CpK)
- Multivariate analysis
- Maintenance of models e.g. NIR, Raman
- MSPC (multivariate statistical process control

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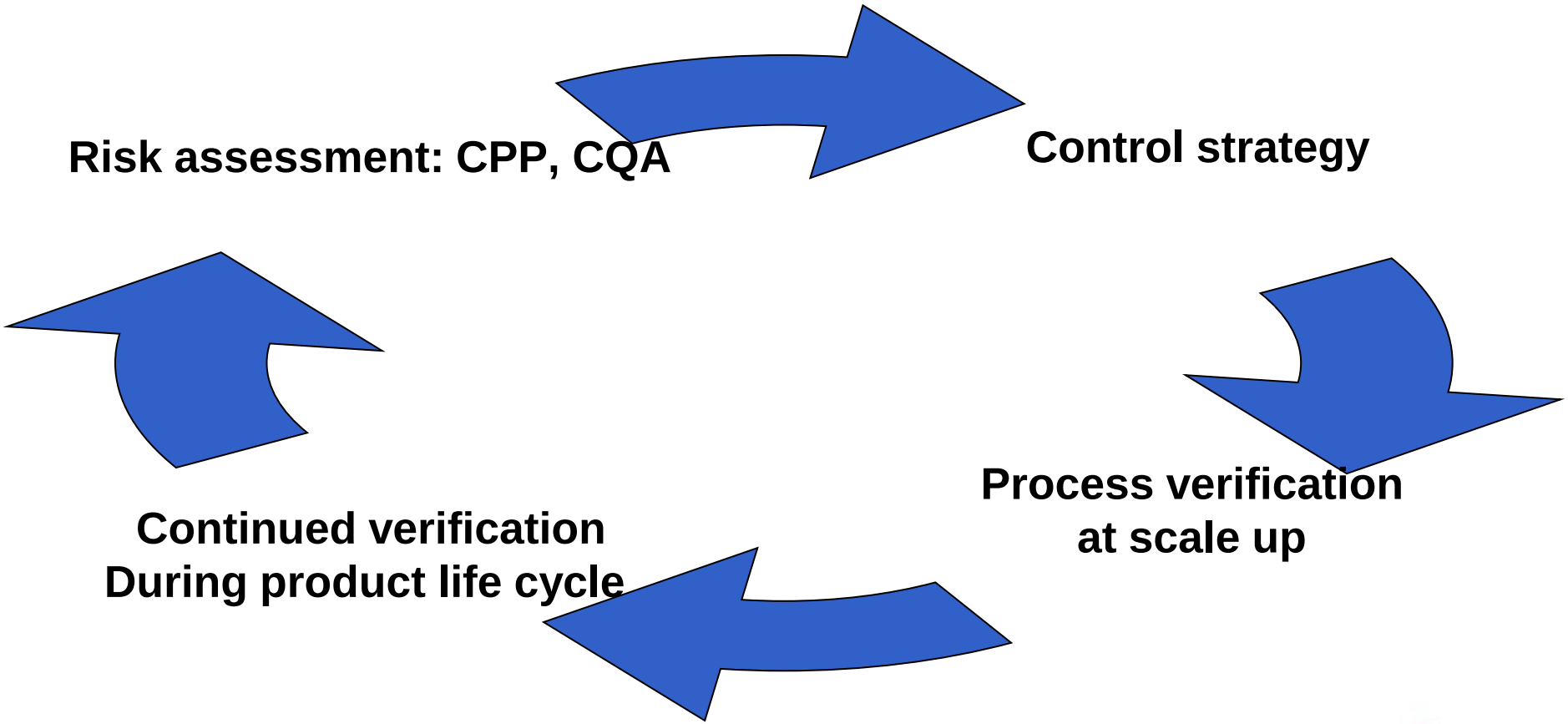
Process validation lifecycle



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To protect and enhance public and animal health through the regulation of medicine, medical devices and healthcare products