

Regulatory requirements and benefits converting to Continued Process Verification

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Magnus and Pharmadule at a glance

Director Regulatory Affairs, formerly scientific coordinator in the Inspections Sector , EMA
Responsible for Registration and Quality Management for both manufacturing and R&D-projects

- Pharmadule
  - Established in 1986
  - Acquired by Morimatsu Group in 2011
  - Has built >60 Pharmaceutical facilities
  - Big Pharma – Worldwide
  - 5 facilities in China
  - Full scope
    - Facilities
    - Regulatory Compliance

Stockholm



Shanghai







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Agenda

- What is Process Validation
- Continued Process Verification
- Conclusions

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Definition

Process Validation EU:

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.

Process Validation FDA

The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

New approach to PV – Continuous/continual …

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

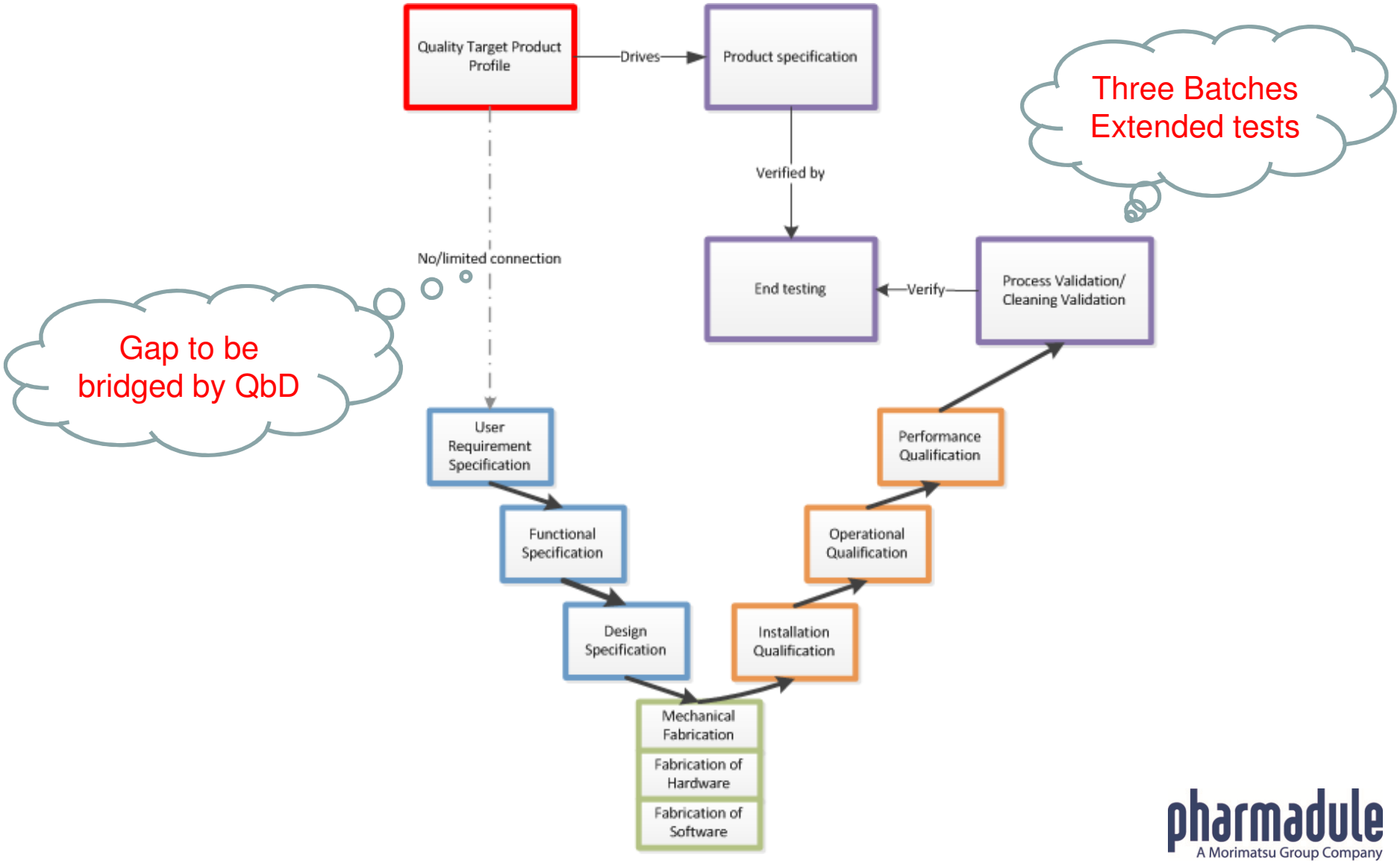
Continued Process Verification:

Documented evidence that the process remains in a state of control during commercial manufacture (FDA PV guide).

In the draft EU Annex 15 the word ***"on-going"*** has replaced ***"continued"***

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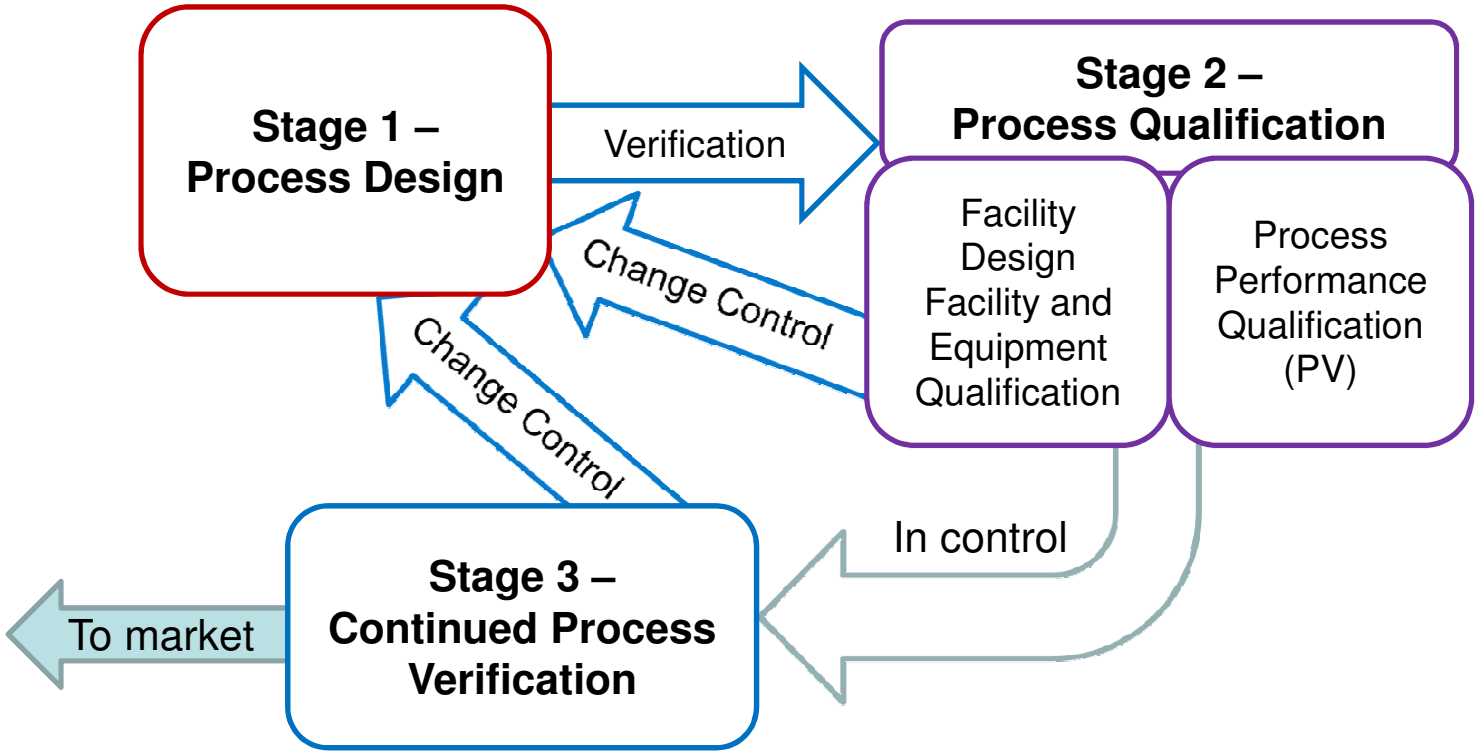
Traditional Process Verification via V-model



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A new approach to Process Validation & compliance

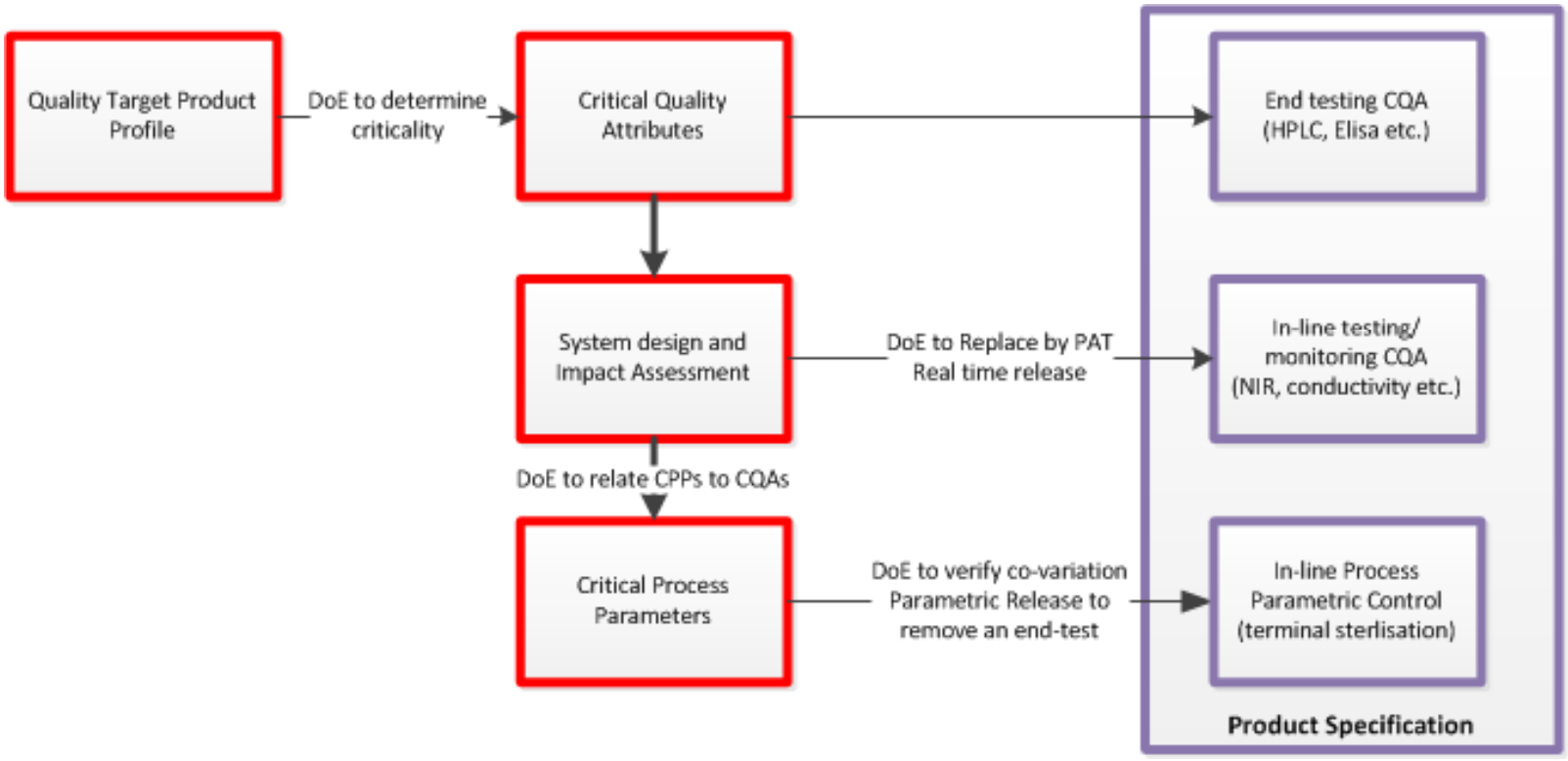
FDA PV - From Process Design throughout Continued Process Verification



References: FDA Process Validation: General Principles and Practices
EMA Guidelines for GMP Annex 15 (draft issued February 2014)

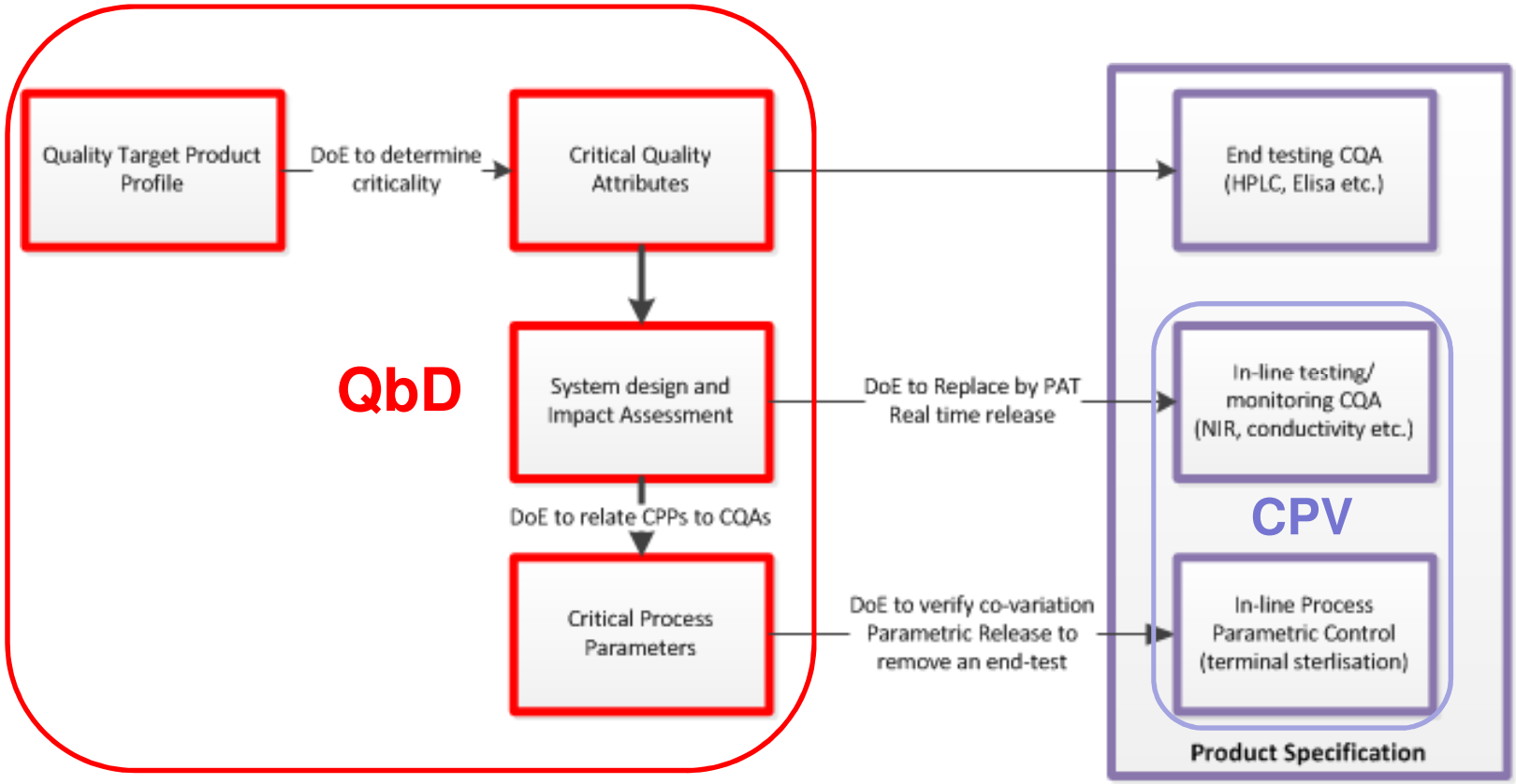
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QbD and Continous Process Verification



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QbD and Continous Process Verification



Hybrid Specifications may be the future

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New EU variations regulation

B.II.g) *Design Space and post approval change management protocol*

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for excipients/intermediates and/or the finished product.		**1, 2, 3**	**II**

Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

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In the future: Continued Process Verification

May be an option

- Under which conditions?
- How can it be achieved?

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ICH Q10 – Pharmaceutical Quality System 2008

Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches *

*Note: This annex reflects potential opportunities to enhance regulatory approaches.

The actual regulatory process will be determined by region.



Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.



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Pharmaceutical Quality System (EU GMP)

Product Quality Review

§1.10

Regular periodic or rolling quality reviews of all authorised medicinal products should be conducted with the objective of **verifying the consistency of the existing process**, **the appropriateness of current specifications** for both starting materials and finished product, **to highlight any trends** and to identify product and process improvements.

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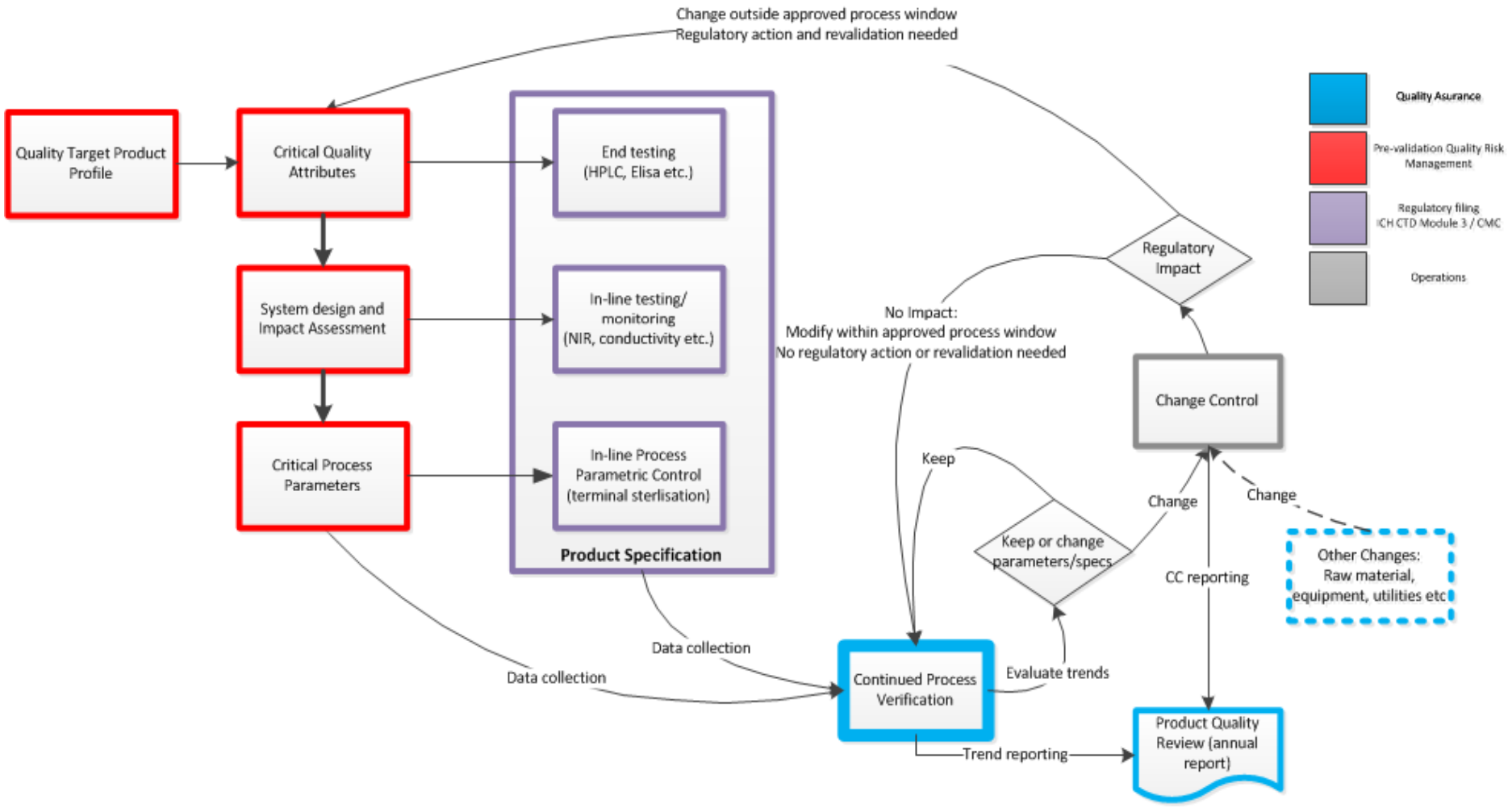
Pharmaceutical Quality System (EU GMP)

§1.11

The manufacturer should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the **Pharmaceutical Quality System**

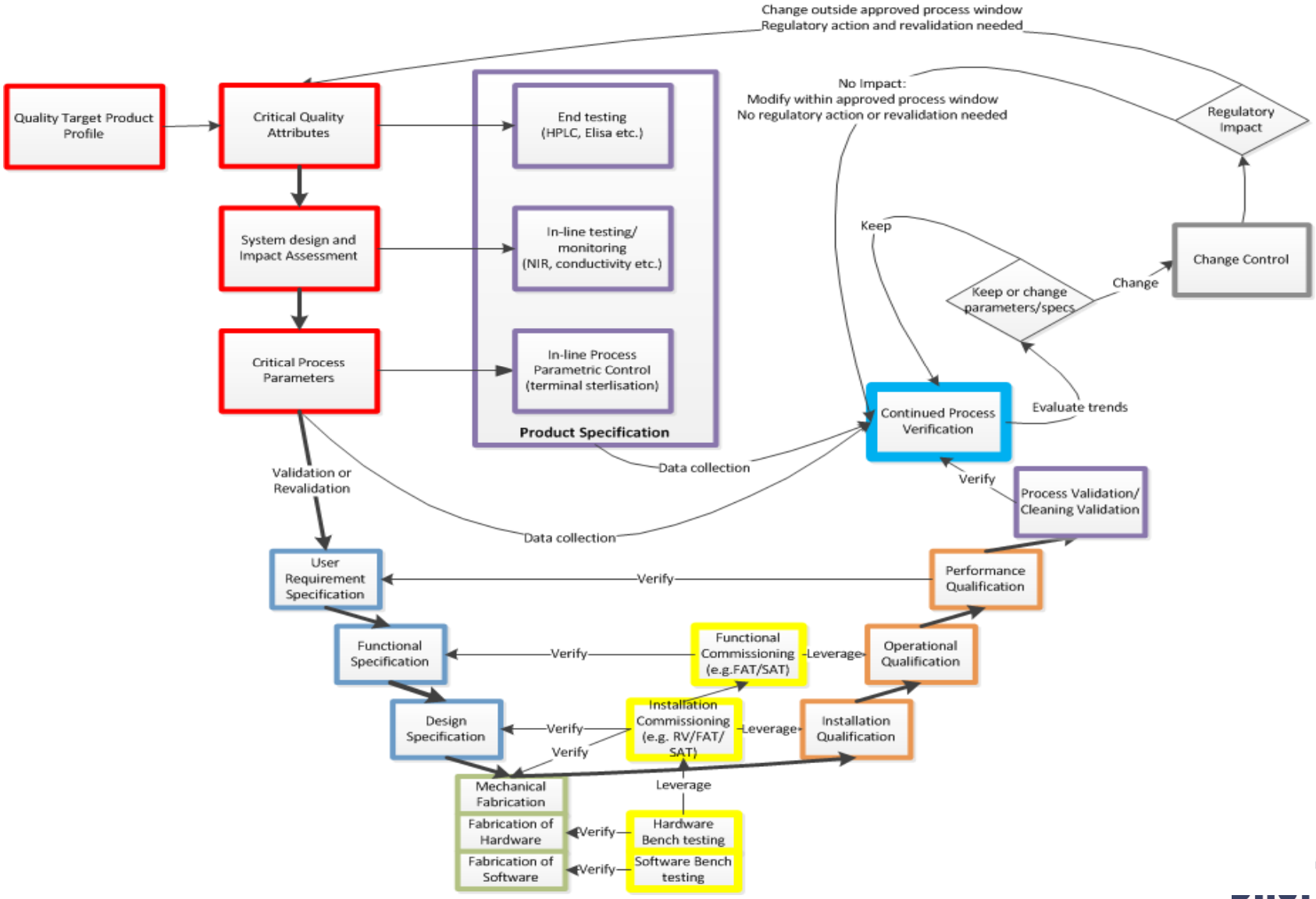
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Continued Process Verification – During Life Cycle



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Total PV and CPV life-cycle model



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How to record Continued Compliance

- Quality System
- Change control (as mentioned before)
- Annual Product Quality Reviews
- Risk and science-based PV (but not necessarily QbD/Continuous Process Verification)

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Conclusions

- Continued Process Verification
  - Can be done without variation registration
  - Requires Quality management system
    - Change control
    - Product quality reviews
    - Science and risk based process control

Implementing Continued probably makes more business sense than registering Continous …

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Thanks for your attention
Questions?



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