Setting Specifications

How and Where to Control

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on behalf of EBE
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Specifications – *Presentation outline*

- Monitoring of Critical Quality Attributes (CQAs)
- Testing
  - Types of testing
  - Types of acceptance criteria
- Handling of CQAs and non-CQAs

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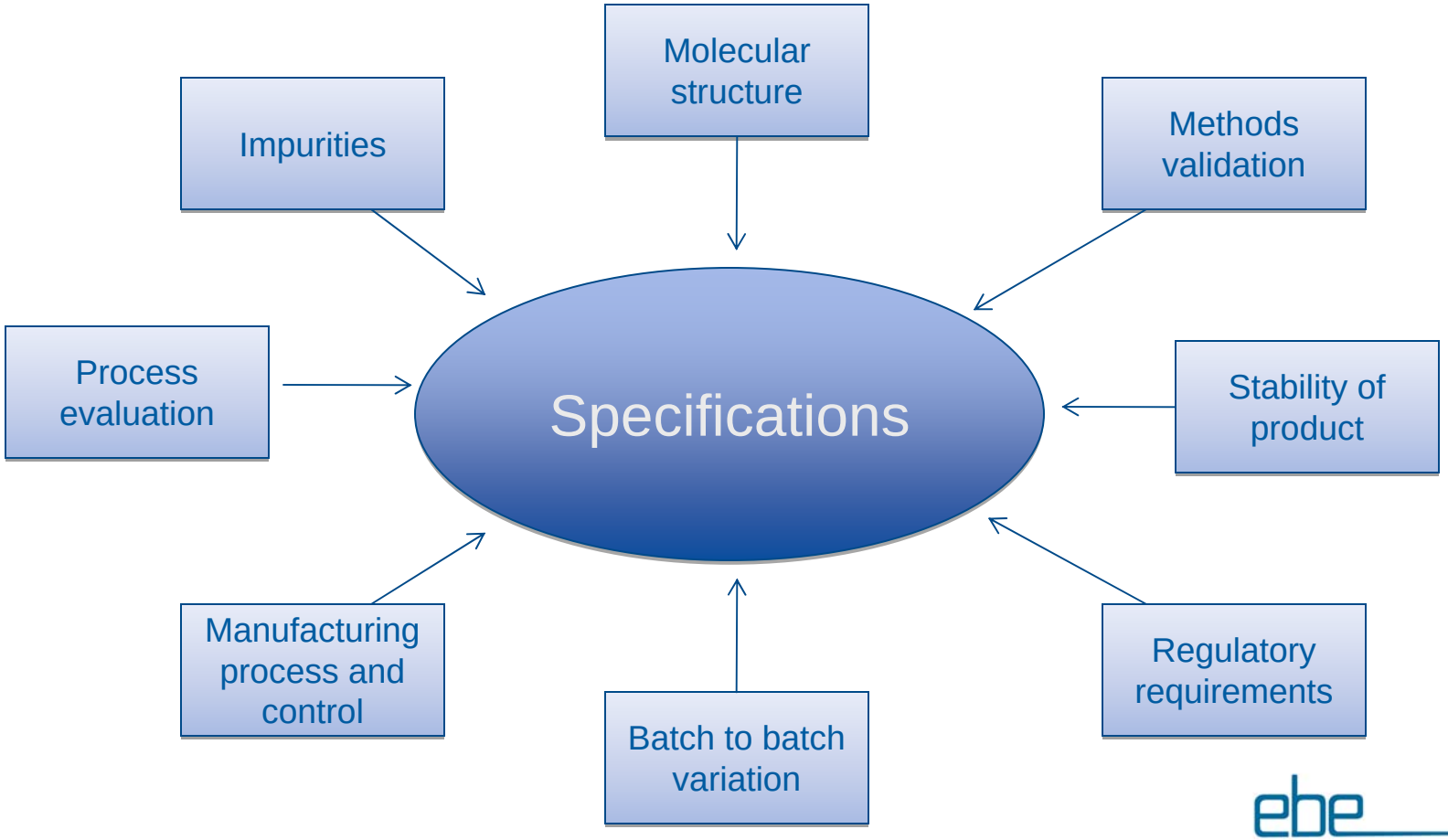
Rationale for Setting Specifications



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Starting point - *for setting specifications*

- The ideal case
  - No Critical Quality Attributes have been identified
  - Stable and robust process has been established

Drug Product Specifications

Attribute	Test
Identity	Suitable method
Potency	Relative activity
Content	A_{280}
Purity	Endotoxins
Safety	Sterility

- The real case
  - Add each CQA identified
  - Select a suitable method

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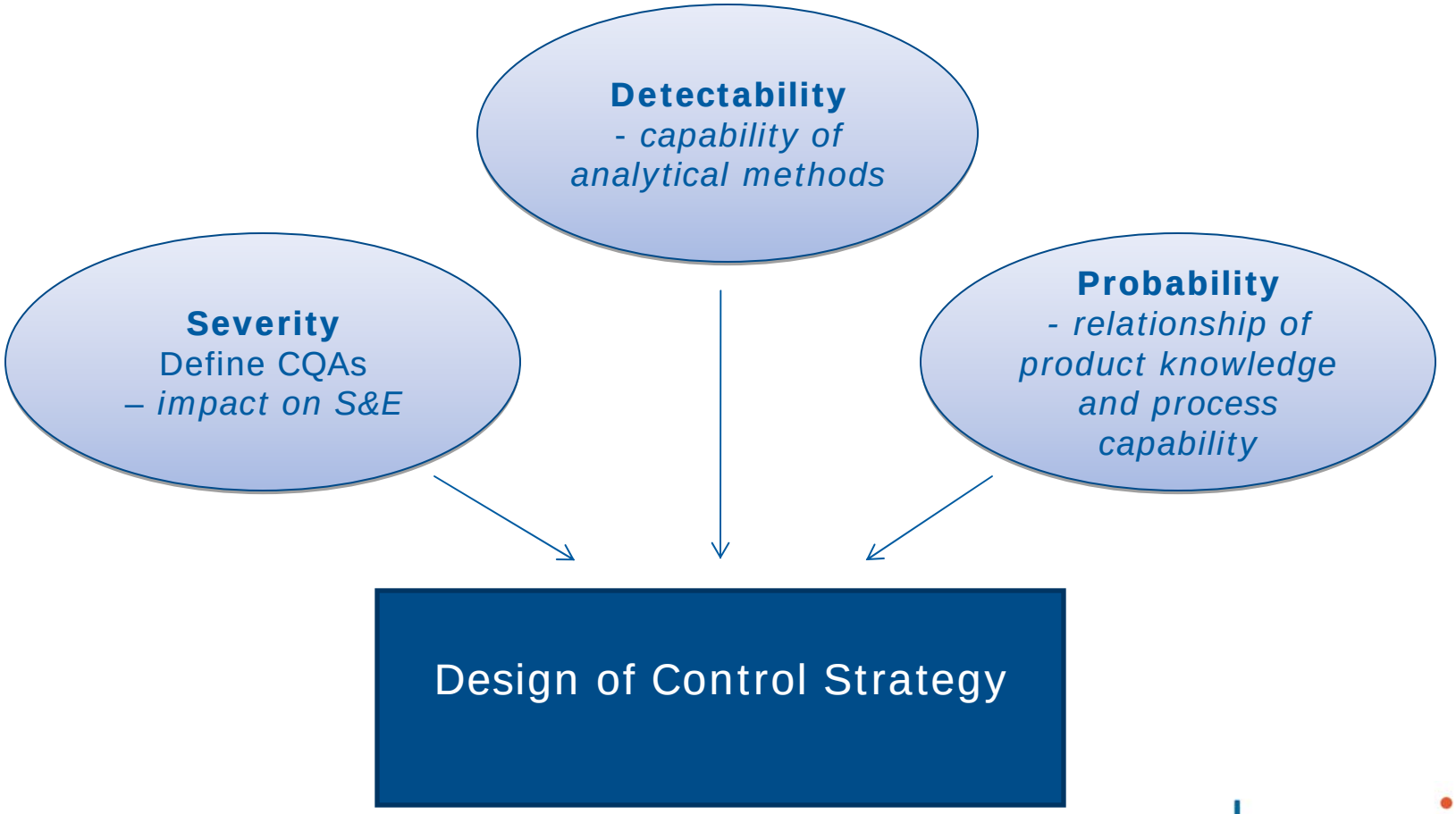
Risk Assessment - *for control of CQAs*



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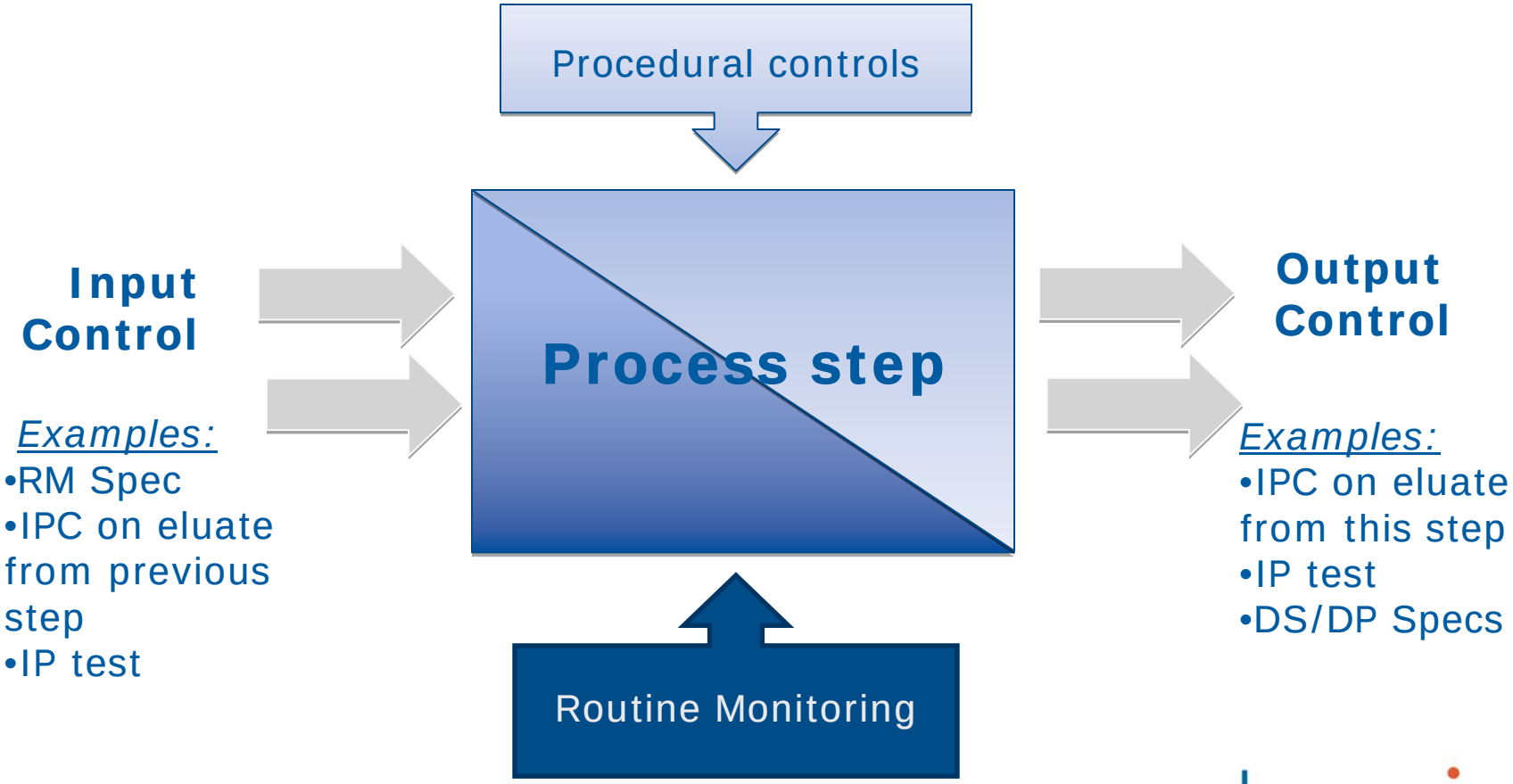
Control Strategy – *for each step and the process*



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Testing - *for routine monitoring of QAs*

1. In Process Controls (IPC)
   - Confirm QAs on each batch
   - Control input for next step
   - Real Time Release Testing (RTRT)

2. End Product Testing
   - Drug Substance and Drug Product
   - Skip lot testing

3. Life cycle management
   - Real time stability monitoring
   - Accelerated stability testing
   - Comparability testing

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Example – *Real Time Release Testing*

- Mab – Oligosacharide profile
  - *Criticality assessment*
    - Impact on: Biological activity / Immunogenicity / Clearance?
  - *No - attribute is NOT a CQA – no routine monitoring required*
  - *Yes - attribute is a CQA - should be monitored*

- Prior knowledge
    - Glycosylation is formed during cell culture production and doesn't change during down stream processing or storage

- In-Process testing in lieu of End Product testing
    - CQA testing is performed on the harvested bulk
  - Report result
    - In process Control in Batch records
    - On Certificate of Analysis with reference place of testing

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End Product Testing – *DS vs DP*

- Drug Substance vs Drug Product testing

  - No DS release testing required
    - Direct filling of Purified DS
    - DP Certificate of Analysis includes testing of all CQAs

  - DS release is required if
    - Storage of DS before fill
    - Pooling – release testing to confirm product quality before mixing of several batches

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Life cycle management – *testing strategy*

Specification Testing

- Stability testing
  - Shelf life specifications
  - Routine monitoring on a periodic basis
- Comparability testing
  - Assessment of impact after process changes

Investigational Testing

- Forced degradation study / Accelerated stability
- Initial assessment of the molecular capability and understand the degradation pathway
- Selection of stability indicating methods
- Identify critical condition in the process
- Formulation development

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Types of Acceptance Criteria

Examples

- Quantitative
  - Range
    < X <
  - "Open ended"
    Not More Than
    Not Less Than

Protein Concentration:
10 ± 1 mg/mL

Host Cell Protein:
< 10 ppm

- Qualitative
  - Compare to reference material

Identity:
Profile comparable to
Reference Material*

* To a well characterized Reference Material

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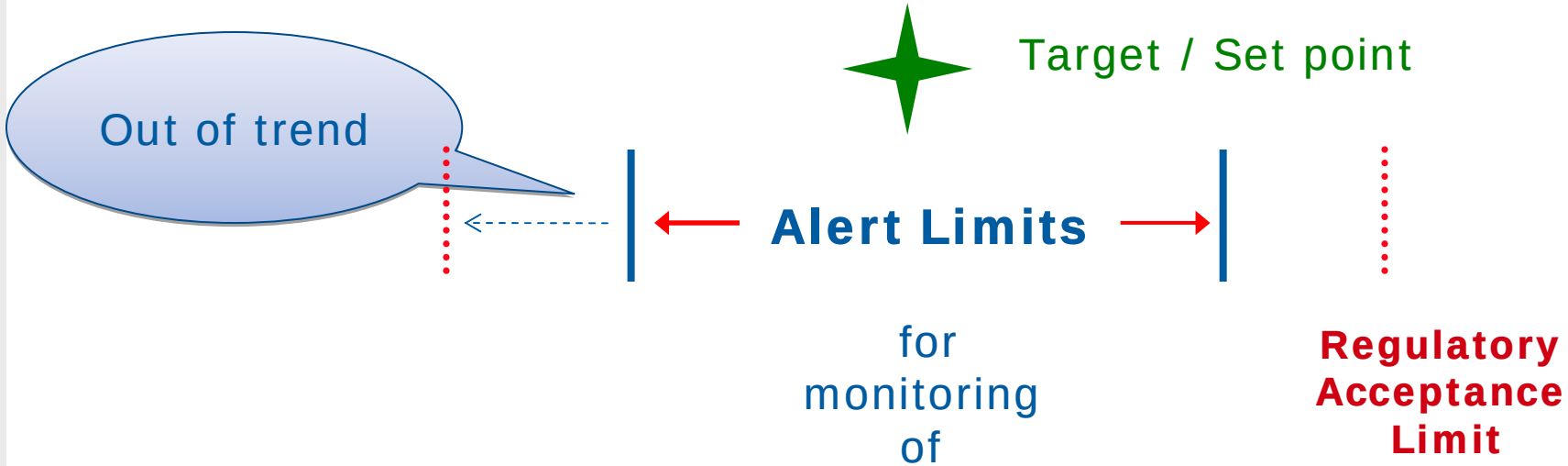
Quantitative Acceptance Criteria



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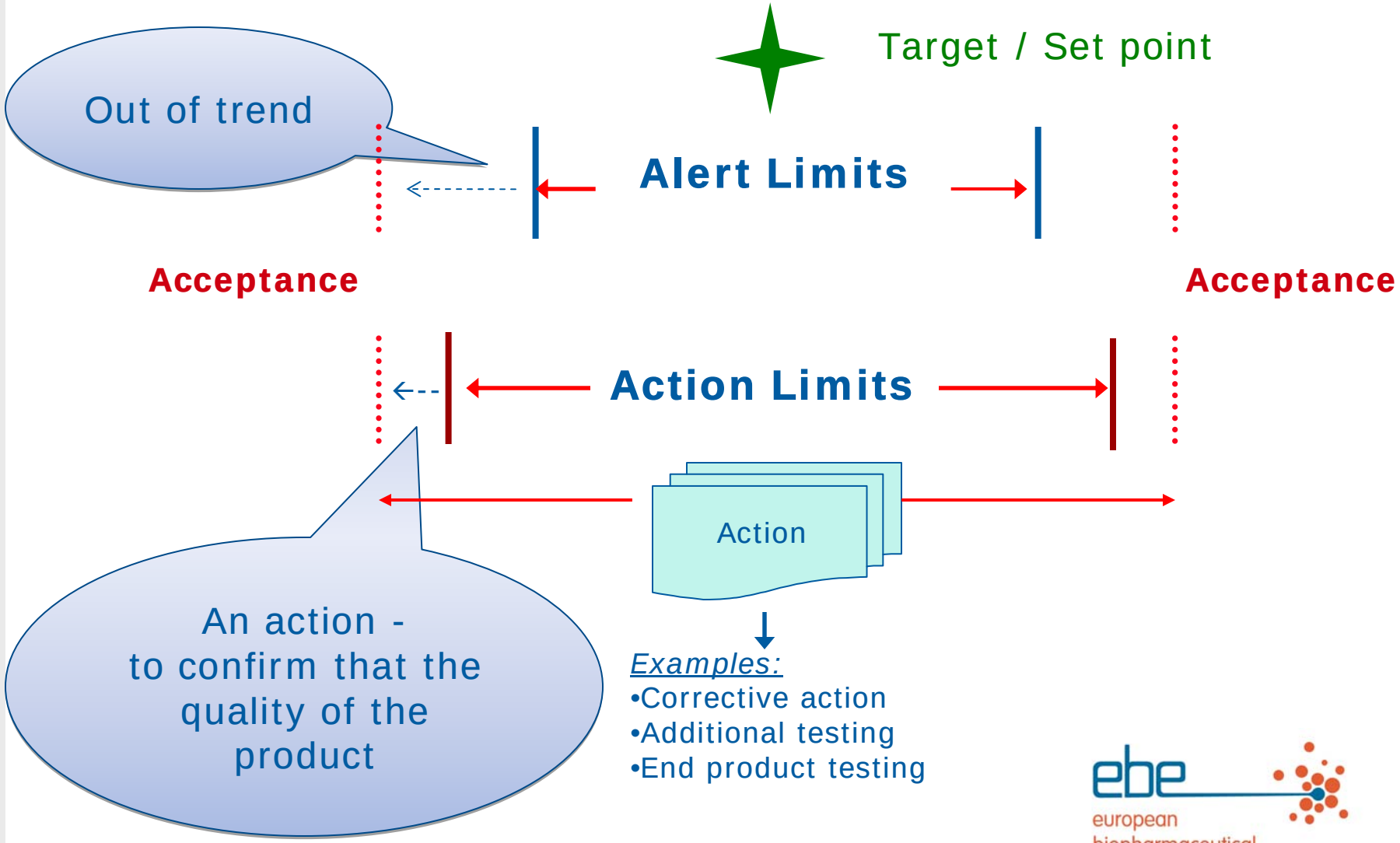
Quantitative Acceptance Criteria



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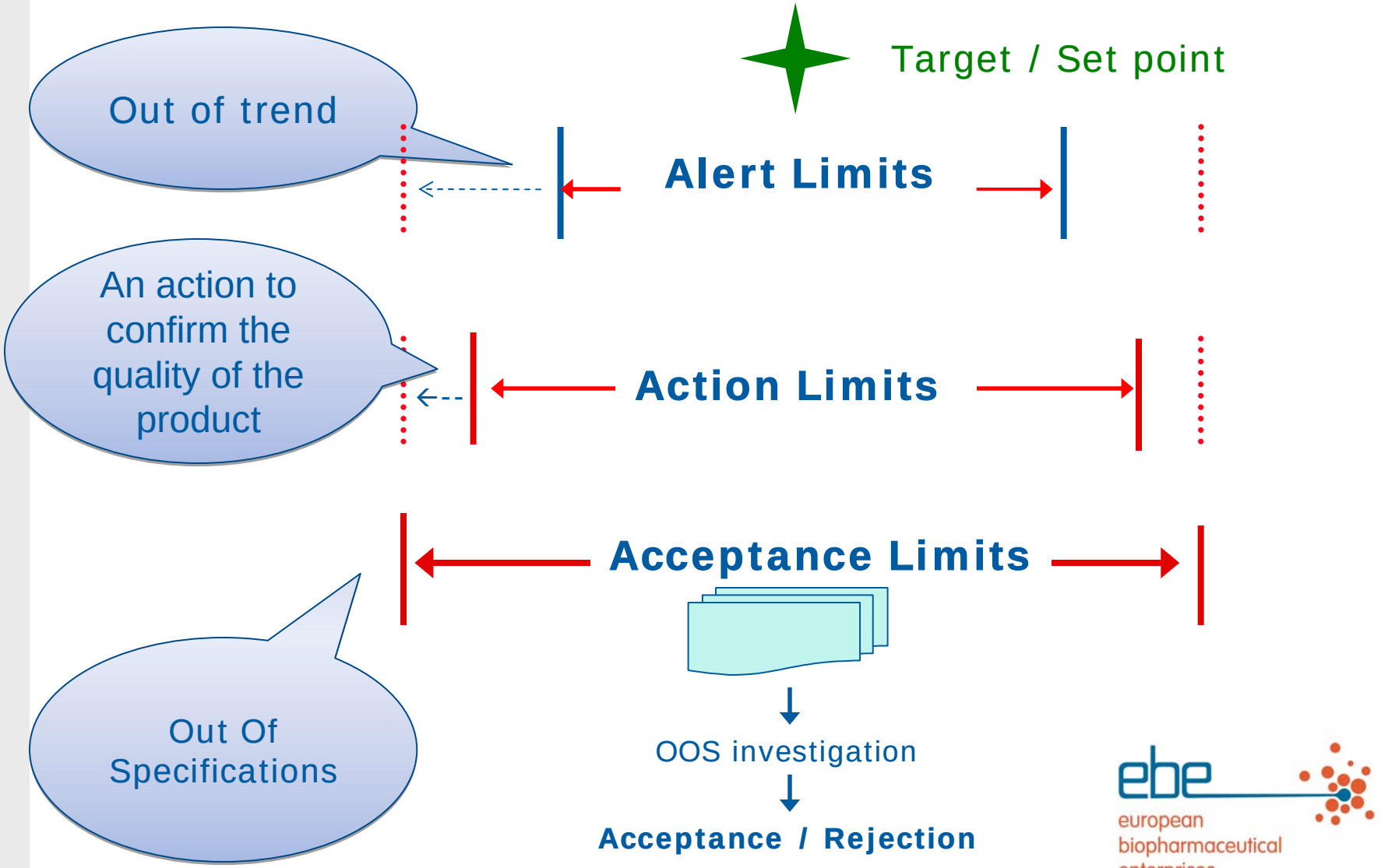
Quantitative Acceptance Criteria



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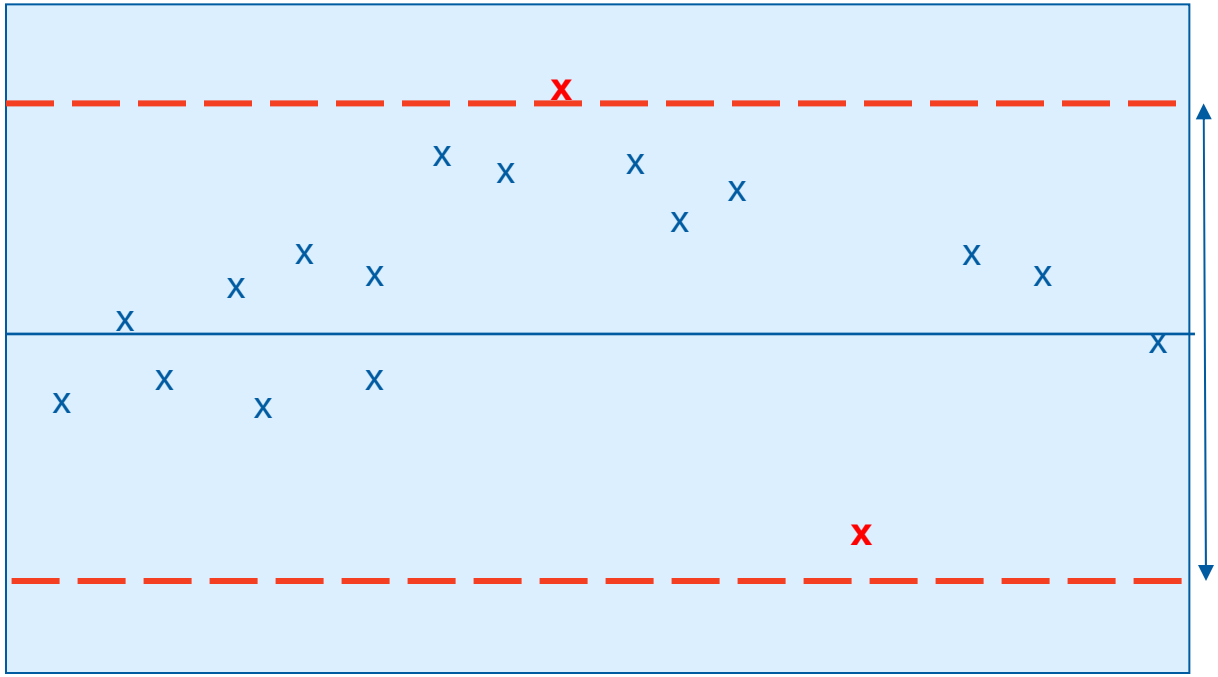
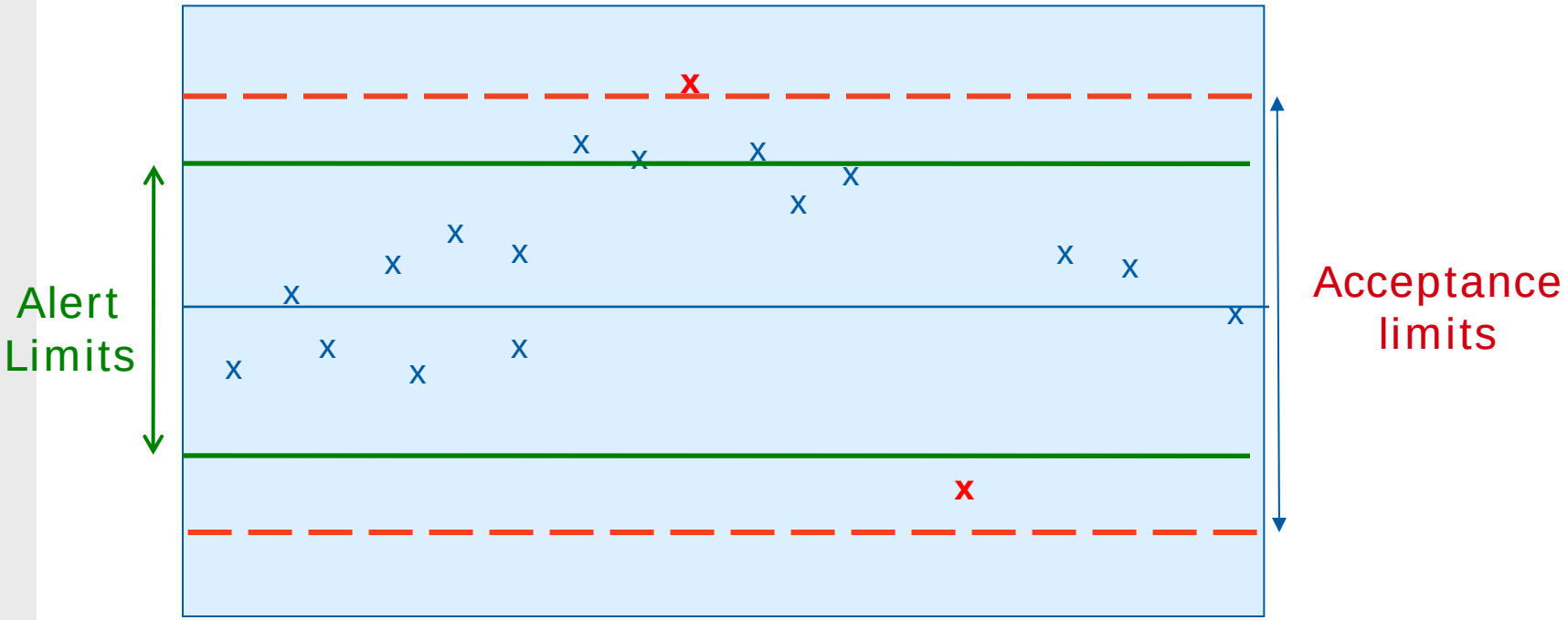
Example - *alert limits*

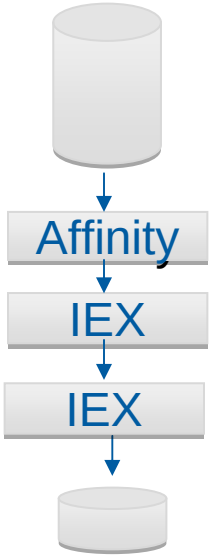


Example - *alert limits*



Example - *action limits*

Control of HCP



DS Bulk

Process Validation	In Process Control	Action
> 500 000 ppm		**if**
5 – 10 000 ppm	< 10 000 ppm	> 10 000ppm
1-200 ppm		
5-8 ppm		
< 10 ppm		

End Product Testing
< 10 ppm

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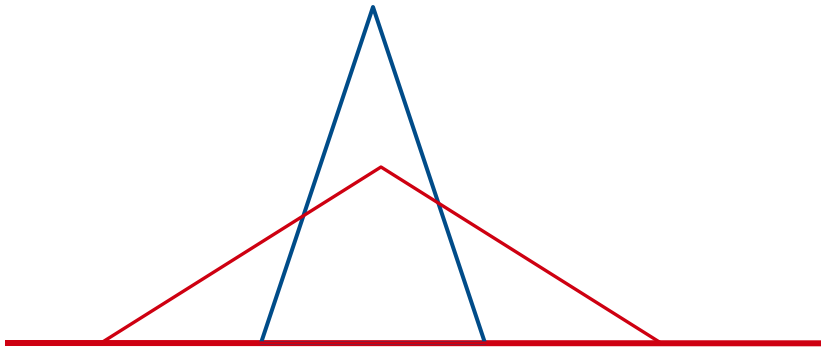
Process vs Clinical Experience

- Experience vary between companies

Example 1

One company has a more consistent process than another company

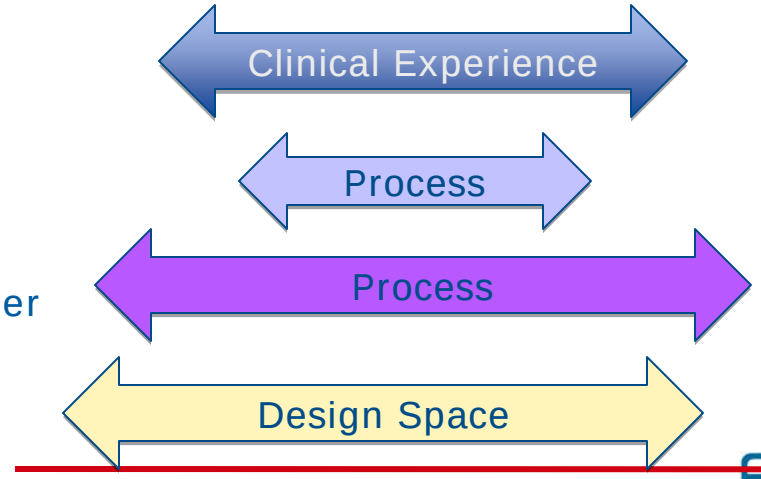


Example 2

Clinical experience is broader than

Consistency batches
or
Consistency batches are broader than clinical experience

Design space different



What are the right specifications?

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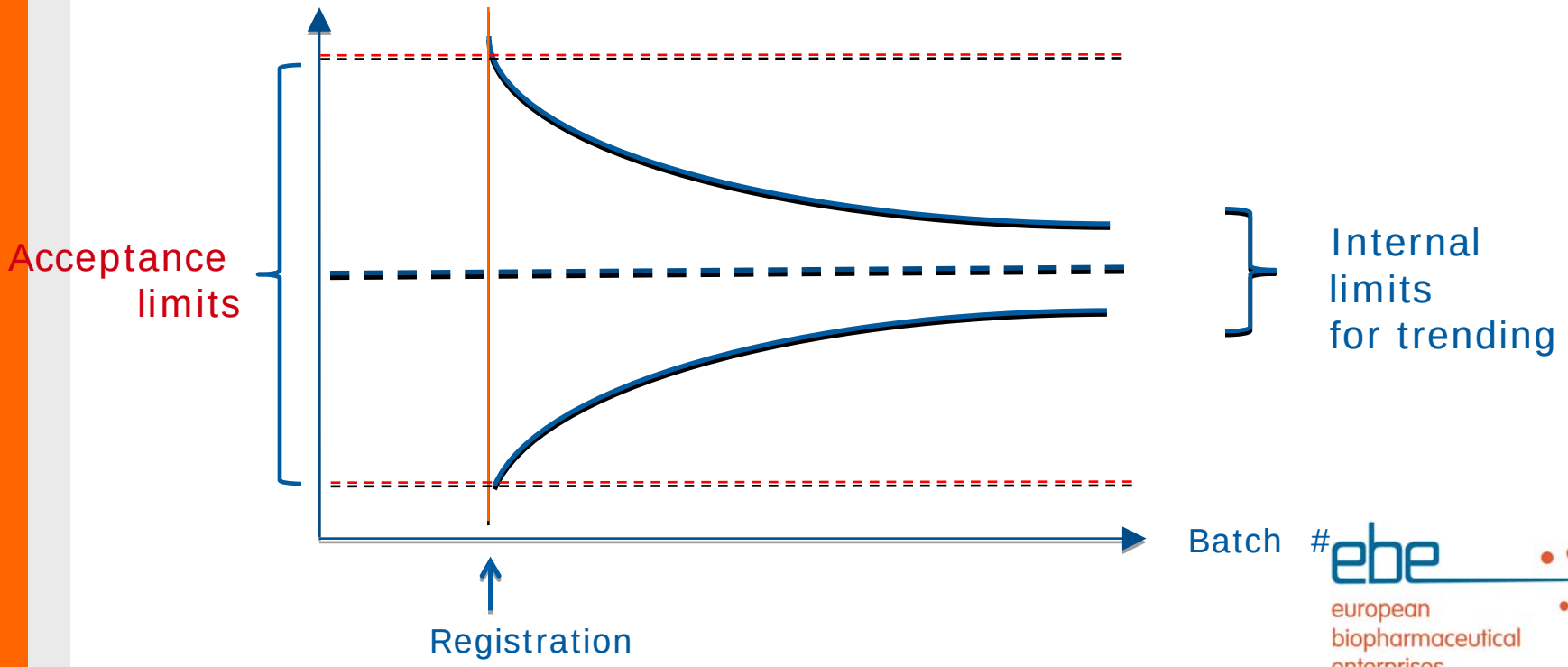
Handling of QA:s - *monitoring*

1. Consistency for ***Non-Critical QAs***
   - Process performance – internal monitoring

2. Clinical limits for ***Critical QAs***
   - Within regulatory limits



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Summary

- A strategy was presented for selection critical quality attributes (CQA) and for selection of type of test to use for a specific attribute (IPC or end product testing)
- Acceptance criteria for regulatory specifications should be based on clinical experience and process capability
- The process for performance should be monitored using internal limits without regulatory commitment

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