Joint BWP / QWP workshop with stakeholders in relation to **prior knowledge and its use in regulatory applications**

How to Use Prior Knowledge in Defining the Control Strategy

EMA, London; 23 November 2017

efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

EMA Prior Knowledge Workshop

Prior Knowledge in an Integrated Control Strategy: *General Considerations*

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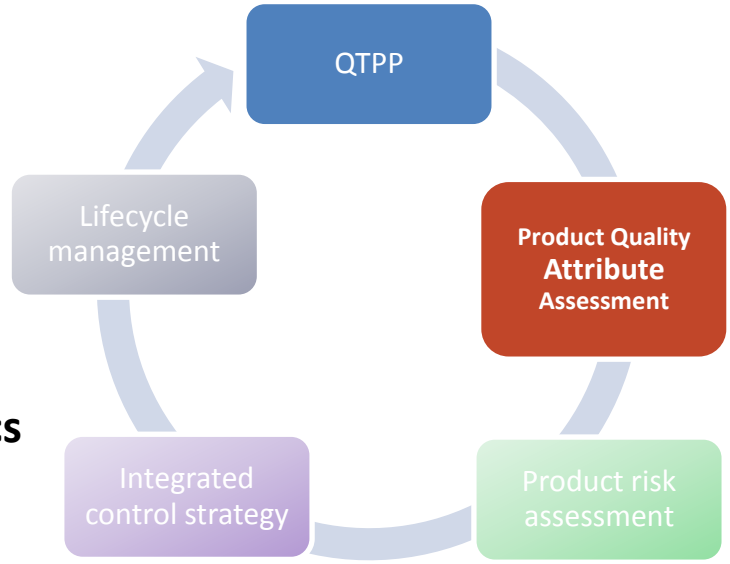
General Considerations: Outline

- **Prior Knowledge in the determination of attribute criticality and appropriate control**
  - **Impact of CQA on product safety and efficacy**
- **Using Prior Knowledge to derive and support clinically relevant specifications**
  - **CQA safety thresholds**
  - **Consequences of tight specification criteria**
- **Case Studies:**
  - **Biologics; vaccines**
  - **Synthetic oligonucleotides**
  - **Biologics; monoclonal antibodies**
  - **Biologics; biosimilars**

Prior Knowledge in an Enhanced Approach to Designation of Critical Quality Attributes

Risk-based approaches to a control strategy uses prior knowledge combined with product-specific knowledge to determine attribute criticality

(Severity of harm)



Scores identify CQAs:

- **Evaluation of impact on immunogenicity, toxicity** *(Safety)*
- **Evaluation of impact on potency, pharmacokinetics** *(Efficacy)*
- **Monoclonal Antibody Case study**

Prior Knowledge may be used to Identify CQAs

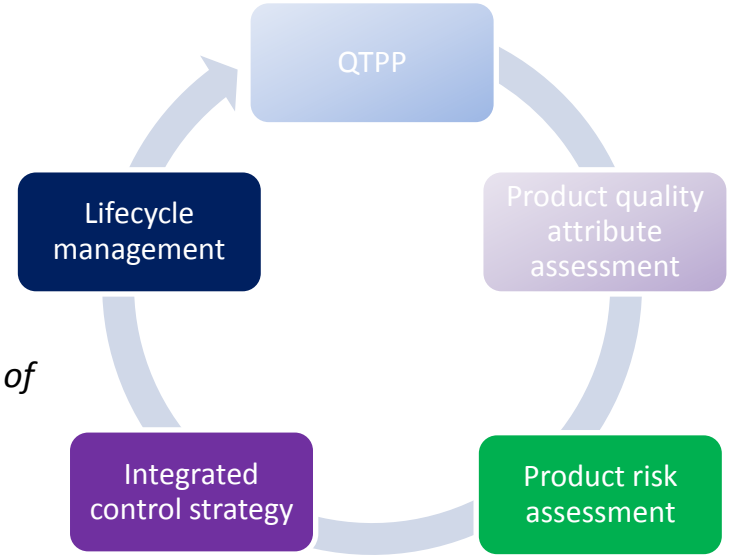
Prior Knowledge in Design of the Control Strategy

Attribute criticality combined with process capability and testing through product lifecycle, determines the appropriate 'integrated' control strategy

Risk = Severity x Occurrence x Detection

Occurrence: *Probability of attribute content falling outside of PAR (process control level, capability)*

Detection: *Test method(s) capability to detect attribute and points of control*



Points of Control are selected to determine a strategy per attribute that minimises risk without redundant testing

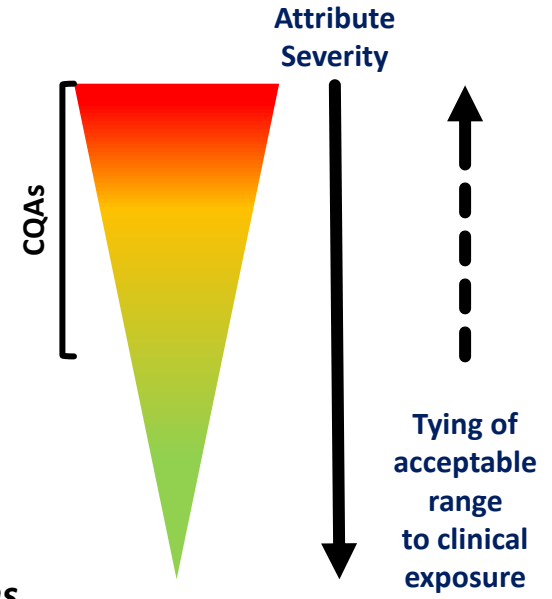
e.g. end-product testing, in-process, non-routine testing

Prior Knowledge is used to determine an attribute control strategy that retains safety and efficacy

Prior Knowledge in Supporting a Specification

1. **The release specification can be determined through Prior Knowledge of which attributes to control**
   - **CQAs may be tested end-product and/or in-process**

2. **Prior Knowledge may set a specification criterion, or justify limits, exceeding the clinical-exposure level while maintaining safety**
   - **Attribute dose ranging using similar molecules for safety thresholds** (model systems)
   - **Weighting of specification factors according to criticality** (risk-based)
   - **Critical when batch data are limited.**
     - ***Avoids rejecting otherwise good batches***
     - ***Allows flexibility for shelf-life extension and storage conditions***
     - ***Facilitates manufacturing site transfers and process changes***
     - ***Can allow faster patient access***



3. **Consequentially, wider criteria requires that less reliance is placed on specification to assess batch consistency and comparability**
   - **The specification should be set focusing on patient safety and not product consistency**
     - ***Consistency could be discussed in Batch Analyses section***
     - ***Trending monitored within the Quality Management System***

Risk-based Clinically Relevant Specifications retain Safety and Efficacy

Current and Future States for Use of Prior Knowledge

Currently, reporting of Prior Knowledge is limited to assigning criticality:

- Mostly gross extrapolation across products and theoretical impact on PK and immunogenicity, e.g. literature
- Minimal reporting in dossiers

Short/medium term future:

- Prior Knowledge data from similar molecules to assess immunogenicity, using in vitro and in vivo models
- Apply QbD principles of ICH Q8/Q10
- More upstream translation of testing from end-product testing to in-process testing
- Reduced testing of certain 'historical' CQAs (e.g. residual DNA, HCP)

Longer-term future, through experience, more attributes generally regarded as safe, driven by Prior Knowledge evidence:

- Removal of GRAS attributes from routine control
- Use of safety thresholds to justify release specifications exceeding clinical exposure

Prior Knowledge has potential for greater use in determining a risk-based control strategy

Prior Knowledge in the Control Strategy - Question

What would it take for prior knowledge (from similar molecules or across families of products) to be considered as acceptable in defining acceptance criteria that are not specifically tightened to attribute clinical exposure?

- *Justified prior knowledge can be extrapolated to new molecules for well understood modalities and product quality attributes.*
- *The specification should assure safety and efficacy, and a risk-based approach may be used to determine the amount of information needed to qualify the prior knowledge*
- *Batch consistency may be assured in the Batch Analyses sections and the QMS*