Quality by Design (QbD) for
Pre-Filled Syringes (PFS)

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What?

- A systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control based on sound science and quality risk management. [ICH Q8]
Why?

• Protect the patient.

• Ensure that marketed batches have the same safety & efficacy profiles. Risk to the patient is minimised by decreasing variability.

• Goal: process that is insensitive to disturbances. Robust.
“Ultimate success (for industry and regulators) is having affordable drugs for the patient.”

“Industry, academia and FDA must work together to find ... less costly ways to turn good biomedical ideas into safe and effective treatments.”
Sterile products are minority dosage forms.
Manufacturing process is extremely critical.
Utilisation of PAT and QbD for sterile products so far is still limited.

The Agency strongly encourages the use of the QbD concept, but stability testing would continue to be part of a regulatory submission.
Free of contamination, reproducibly delivers the therapeutic benefit promised in the label to the consumer. Dr J Woodcock CDER
### QbD

<table>
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<tr>
<th>QTTP</th>
<th>CQAs</th>
<th>Risk</th>
<th>Design space</th>
<th>Control strategy</th>
<th>Continuous improvement</th>
</tr>
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<tbody>
<tr>
<td>• Dose form, delivery system.  • Strength.  • Container closure.  • Sterility, purity.</td>
<td>• Potential CQAs.  • Purity, particle size, sterility, bulk density, viscosity, .</td>
<td>• Prioritise.  • FMEA.</td>
<td>• CPP.  • Map ...  • Material and process variables.  • to ...  • CQAs  • Design of Experiments.  • Multivariate.</td>
<td>• In-Process Controls.  • Product specifications  • Sterilisation parameters.  • Bio-burden control.  • PAT</td>
<td>• Reduce variation to target values.  • not...  • Response to CAPA.</td>
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</tbody>
</table>

#### Required
- Quality Target Product Profile
- Product understanding
- Process understanding
- Control strategy & justification

#### Optional
- Design space
- Process Analytical Technology
The Concept of Quality-by-Design - Design

Mark A. Staples

QbD System

Define product

Identify product CQAs

Design formulation & process, meet product CQAs

Understand impact on product of materials and process parameters

Control: variability in materials and process

Monitor: analyse process variability

Critical Quality Attribute CQA

Product design

Process design

Development

Assess risk

Control risk
The range of possibilities within which process parameters may be varied without compromising product quality over the shelf life of the product.
Design Space

Product–Syringe Interaction and Its Impact on $f_{friction}$
Effects of shear thinning
a. Newtonian
b. non-Newtonian

Effects of temperature
• Storage temperature.
• Operation at low temperature.
• Equilibration time.
Taguchi

- Target product profile
- Product critical quality attributes (CQAs)
- Raw material attributes and process parameters
- Risk assessment
- Design space
- Control strategy
- Lifecycle management and continuous improvement

“IT is just as unethical to add tremendous cost to ensure products are of good quality as it is to ship defective goods.”
Process capability

Specification

Upper limit

Specification

Lower limit

Specification

Upper limit

Specification

Lower limit
Continuous improvement

• Reduce variability.
• Tighten specifications.
• Increase process capability.

Reduce variability about nominal
Vs.
Respond to CAPA.
Robust operation

1. Understand the process – the shape of the function.

2. Find operating conditions under which process and product quality are insensitive to normal variations & disturbances.

3. Set specifications on materials and upstream processes to limit disturbances.

4. Use data – DoE.

Injection time seconds

y = f(x)

Needle diameter
Design robustness
Quality by Design

Control strategy

- Traditional control strategy (fixed controls)
  - Variability in product quality (not affected by design)

- Dynamic control strategy (flexible controls)
  - Variability in product quality (affected by design)

Design space

- Knowledge Sharing: Database and Glossary
- Mechanistic Understanding (in vitro and in vivo)
- Biopharmaceutics Risk Assessment Road Map
- QbP-Driven Specification

Risk assessment

- Inputs to control strategy: Critical quality attributes, Capability of process and analytical methods
  - Criticality of quality attribute
  - Capability of process and analytical methods

- Elements of control strategy
  - Aggregates
  - HCP
- Examples:
  - IPC testing
  - Raw material controls
  - Specifications
  - Product characterization
  - Stability studies
  - Process validation
  - Process monitoring
  - Comparability studies

Roadmap for implementation of quality by design (QbD) for biotechnology products
Anurag S. Rathore

Applied Biopharmaceutics and Quality by Design for Dissolution/Release Specification Setting
Quality by Design

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