Quality by Design (QbD) Overview

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What is Quality by Design (QbD)?

- QbD is:
  - A Quality System for managing a product's lifecycle
  - A regulatory expectation
  - Intended to increase process and product understanding and thereby decrease patient risk
  - A multifunctional exercise
- QbD isn't:
  - New
  - Design of Experiment (DoE)
  - Design Space

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QbD Builds on Past Quality Systems

Principle QbD Concepts:

- Risk and knowledge based decisions
- Systematic approaches process development
- Continuous Improvement
- This leads to "capable" processes

Short Quality Bibliography

- 1979- P. Crosby's *Quality is Free*
- 1982- W.E. Deming's *Quality, Productivity, and Competitive Position* with 14 Key Principles
  - #3- Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place.
- 1986- Motorola develops Six Sigma
- 1987- FDA's first Guideline on Process Validation
- 1988- US DoD implements Total Quality Management
- 1991- J. Juran's *Juran on Quality by Design: the new steps for planning quality into goods and services*
- 2005- ICH QbD related drafts appear- ICH Q8-11
- 2008- FDA's *Guidance for Industry Process Validation: General Principles and Practices* (Rev. 1, 2011)

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QbD is "Woven" into Regulatory Guidance Documents

FDA 2011 Process Validation Guidance

- A "Risk-Based Approach"
  - Process Development
    - Experimental design (DoE)
    - Control Strategy
  - Process Qualification
    - Equipment qualification
    - Process performance qualification (PPQ)
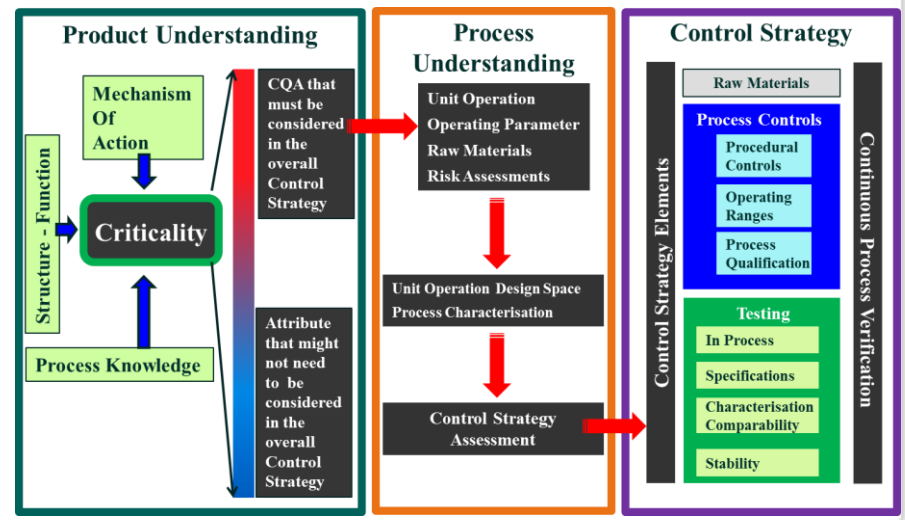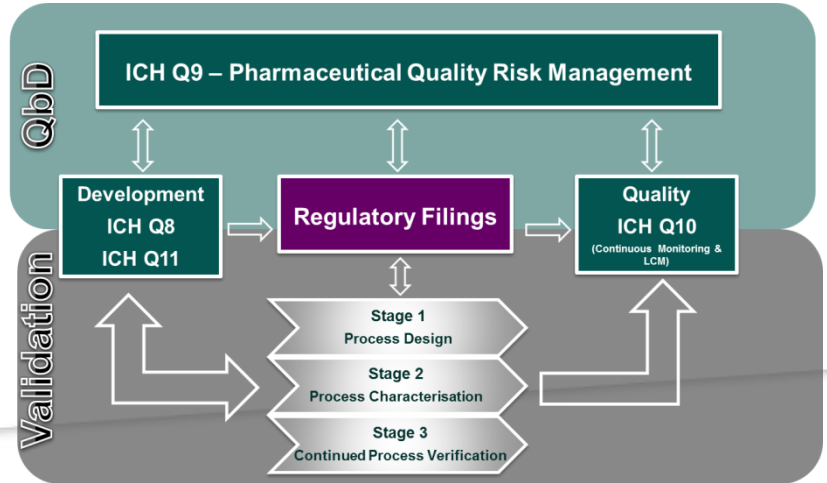 - Continued Process Verification

ICH

- Primarily ICH Q8 through Q11
  - Q8- Pharmaceutical Development
  - Q9- Quality Risk Management
  - Q10- Pharmaceutical Quality System
  - Q11- Development and Manufacture of Drug Substances

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How has industry responded?
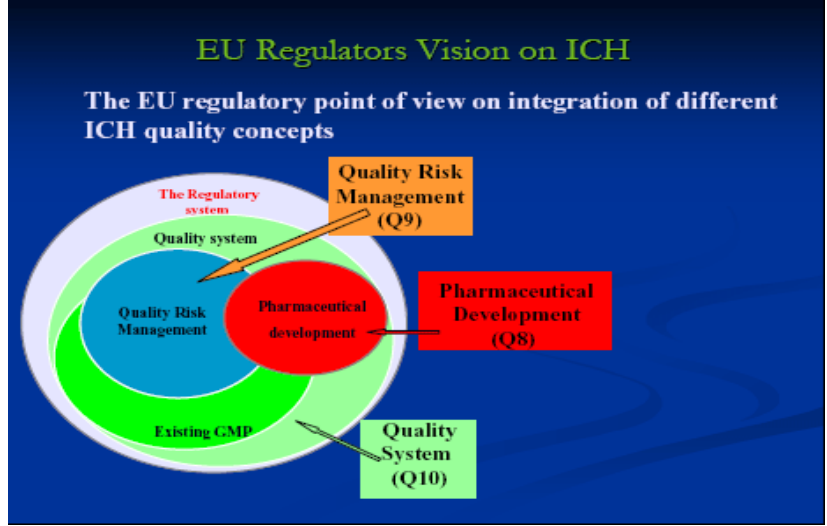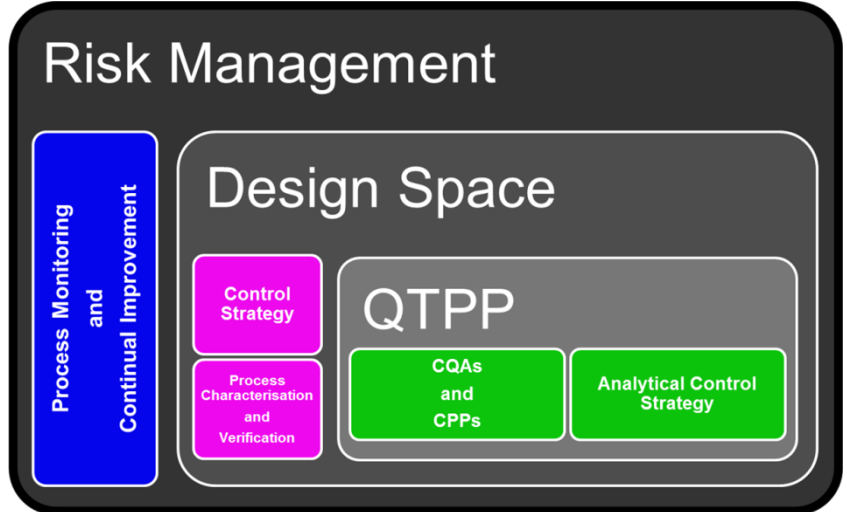
It can be Confusing!

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Understanding QbD

Key

- Document
- Process
- Risk Assessment

Target Product Profile (TPP) → Early Product Development → Quality Target Product Profile (QTPP) → Process Development → Control Strategy → Technology Transfer → Process Risk Assessment → Conformance Manufacturing/ Process Qualification → Continued Process Verification

- Initial Confusion

- Research and discussion

- Reaching understanding:

    QbD is a process defined by documentation requirements

- QbD

    - Is similar to PDCA (iterative)

    - Focuses on risk based approaches

    - Encourages continuous improvement

    - Intends to design capable processes

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Primary QbD Documents

- Risk Assessment Report(s)
  - Performed throughout QbD Process
  - Particularly important to process development
- Quality Target Product Profile (QTPP)
  - Defines the desired product characteristics and sets development goals.
- Control Strategy Summary
  - Defines the process, its inputs and outputs, and how it is controlled.
- PPQ Report(s)
  - Formal verification that the process Control Strategy has been defined appropriately and repeatedly produces the desired results.
- Continued Process Verification (CPV) Reports
  - Assuring that during routine commercial production, the process remains in a state of control (FDA); involves feedback loops into the QbD "process" where intentional process changes and/or observed variability is assessed for risk, characterized, re-validated, etc.

QTPP

Control Strategy

Process RA/ PPQ

CPV

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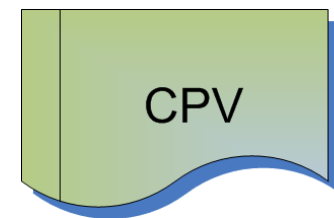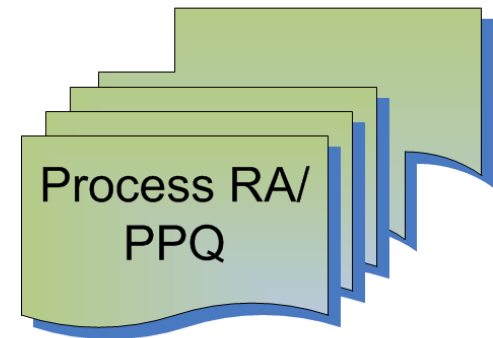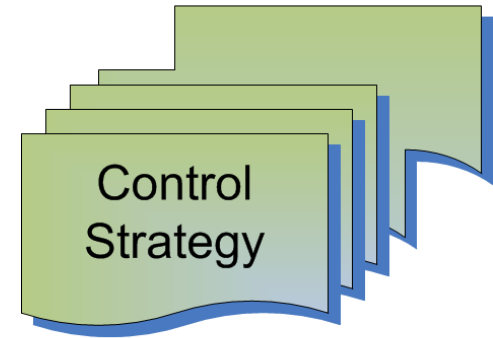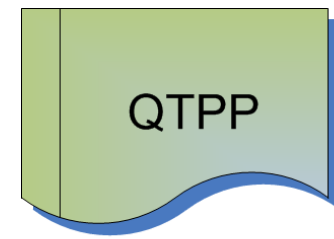
Where Does Risk Assessment Belong?

- QTPP

- Process Development
  - Preliminary CQA/CPP assessment
  - Preliminary raw material/component assessment
- Control Strategy
  - CQA/CPP
  - Raw materials
  - Components (E&L)
- Technical Transfer and/or
- Stage 2 Validation PPQ Protocol Development
- Stage 3 Validation/CPV

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Process Development Risk Assessment

- Performed early in process development

- Defines provisional CQAs

- Establishes known and hypothetical links between raw materials, process parameters and provisional CQAs

- Prioritizes process parameter and material criticality by potential product risk

- Guides subsequent range finding and robustness study design

Manufacturing Stage/ Intermediate Cell Culture to BDI	Appearance	pH	FIX Activity[a]	N-Glycan Profile	Specific Activity	SE-HPLC	CE-SDS for FIX alpha	FIXa	Endotoxins	Bioburden	Residual HCP	Residual DNA	Virus Safety	Comments
Vial resuscitation and inoculum expansion										Z				
Production Bioreactors			Z	X	X	X	X		Z	Z	X	X	Z	
Unprocessed Bulk Clarification (Harvest)				X					X	X	X	X		
POROS HQ50 Anion Exchange Chromatography (Eluate)			Z		Z	Z	Z			Z	Z	Z	Z	
Buffer Exchange by TFF			Z			X			X	Z				
Solvent/Detergent Incubation (Viral Inactivation)			Y										X	
Filtration and Bagging of BDI	Y	Y	Y	Y	Y	Y	Y	Y	Z	Z	Y			

X = Attribute is influenced at this stage, but not tested
Y = Attribute is not influenced at this stage, but tested
Z = Attribute is influenced at this stage and tested

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CQA/Process Parameter Matrix

Manufacturing Stage/ Intermediate	Critical Quality Attributes and Assays													Comments
Cell Culture to BDI	Appearance	pH	FIX Activity[a]	N-Glycan Profile	Specific Activity	SE-HPLC	CE-SDS for FIX alpha	FIXa	Endotoxins	Bioburden	Residual HCP	Residual DNA	Virus Safety	
Vial resuscitation and inoculum expansion										Z				
Production Bioreactors			Z	X	X	X	X		Z	Z	X	X	Z	
Unprocessed Bulk Clarification (Harvest)					X				X	X	X	X		
POROS HQ50 Anion Exchange Chromatography (Eluate)			Z		Z	Z	Z			Z	Z	Z	Z	
Buffer Exchange by TFF			Z			X			X	Z				
Solvent/Detergent Incubation (Viral Inactivation)			Y										X	
Filtration and Bagging of BDI	Y	Y	Y	Y	Y	Y	Y	Y	Z	Z	Y			

X = Attribute is influenced at this stage, but not tested

Y = Attribute is not influenced at this stage, but tested

Z = Attribute is influenced at this stage and tested

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Quality Target Product Profile (QTPP)

- Necessary Elements
    - Quality characteristics: sterility, purity etc. (including specific safety-related impurities where necessary)
    - Pharmacokinetic characteristics: dissolution etc.
    - Therapeutic effect
    - Target patient population: neonate, adult etc., clinical diagnosis
    - Shelf life: temperature, light conditions etc.
- Desired Elements
    - Dosage form: liquid for injection, solid tablet etc.
    - Route of administration: oral, IV, IM, SC
    - Clinical setting: self or clinic administration
    - Primary/secondary packaging: glass or plastic vial/syringe; blister packaging etc
- Other Elements as Appropriate

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The QTPP Leads to Critical Quality Attribute (CQA) Definition

- Critical Quality Attribute (ICH Q8):

  "A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality."

- Potential CQAs are derived from the QTPP and guide product and process development.

- CQAs are identified by quality risk management and experimentation to determine the effect of variation on product quality.

- The CQA list can be dynamic and may be updated based on product and process knowledge.

TPP→QTPP→CQAs→ Specs

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Definition of a process Control Strategy (CS)

- Many CS elements are developed via risk assessments:

  - CQA/CPP, Raw Material, Components, Specifications

- A CS is the final outcome of process development ("Process Design" if using FDA terminology).

- A CS is not a "point-in-time" activity, but rather should evolve as knowledge increases.

- A CS is constituted of many parts, many of which are developed/written at different points in time throughout process development.

  - Exception: for legacy products, all of these various components likely exist in some form and just need to be combined into an integrated control strategy, which can then effectively drive the CPV program.

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Control Strategy Documents

Stage 1: Process Design
- Define the Knowledge Space
- Identify Critical Process Parameters
- Determine the Control Strategy

Stage 2: Process Qualification
- Equipment / Utility / Facility Qualification
- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs

2011 FDA Process Validation Guidance

QTPP

Control Strategy

Process RA/ PPQ

CPV

Control Strategy

Quality Attribute Assessment	Material Specifications	Drug Product Specification
Process Parameter Assessment	In-Process Controls	Manufacturing Narrative
Component Specifications	Packaging Specifications	Storage and Stability

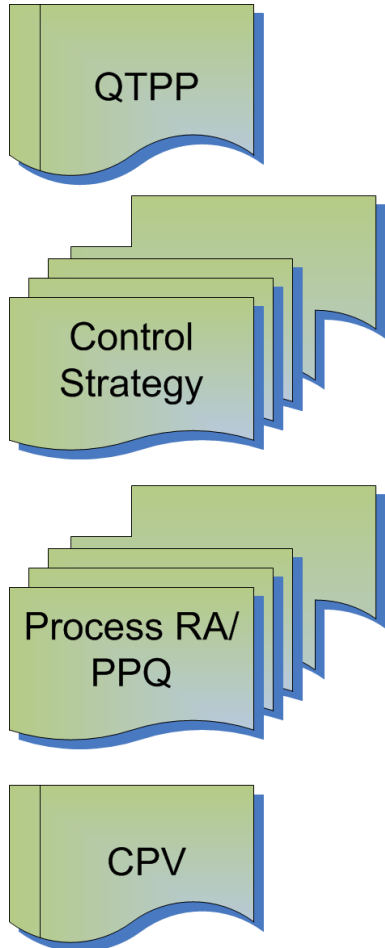Biotherapies for Life™ **CSL Behring**

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Stage 1: Process Design
- Define the Knowledge Space
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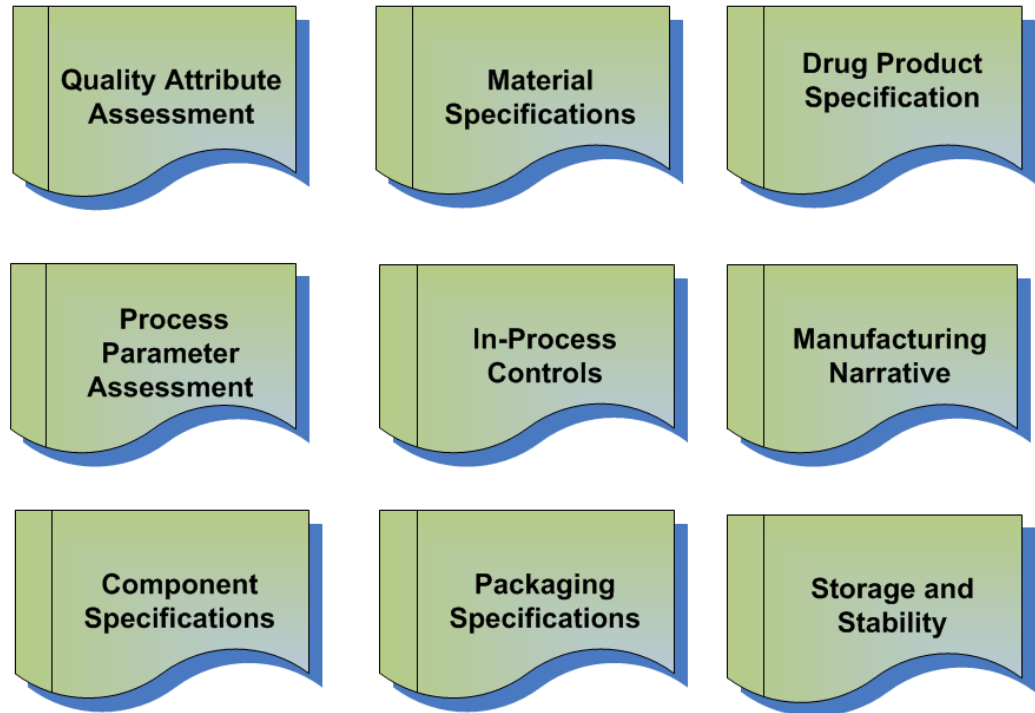
Stage 2: Process Qualification
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- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs

2011 FDA Process Validation Guidance

Process Performance Qualification

- Verification that the defined CS consistently delivers the desired product quality

- PPQ is a significant product milestone

  - Provides proof the process is well controlled

  - Establishes an initial baseline for future process evaluation

- PPQ is a dynamic part of the validation concept

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Routine Manufacturing & Continuous Improvement

2011 FDA Process Validation Guidance

Stage 1: Process Design
- Define the Knowledge Space
- Identify Critical Process Parameters
- Determine Control Strategy

Stage 2: Process Qualification
- Equipment / Utility / Facility Qualification
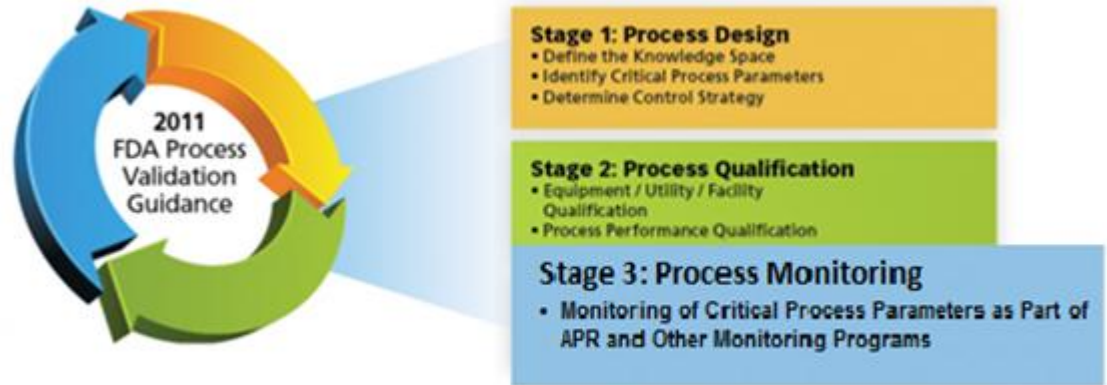- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs

- Continuous Improvement is the last component of the QbD Process

- CPV provides the "feedback" loop in the control of our processes

- Process Monitoring and Evaluation

  - Short Term- IPCs, release criteria

  - Long Term- CPV

- Other components of Continuous Improvement include good integration of process knowledge into change control, deviation management, etc.

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Knowledge management via QbD reduces risk

Product Risk

Process Knowledge

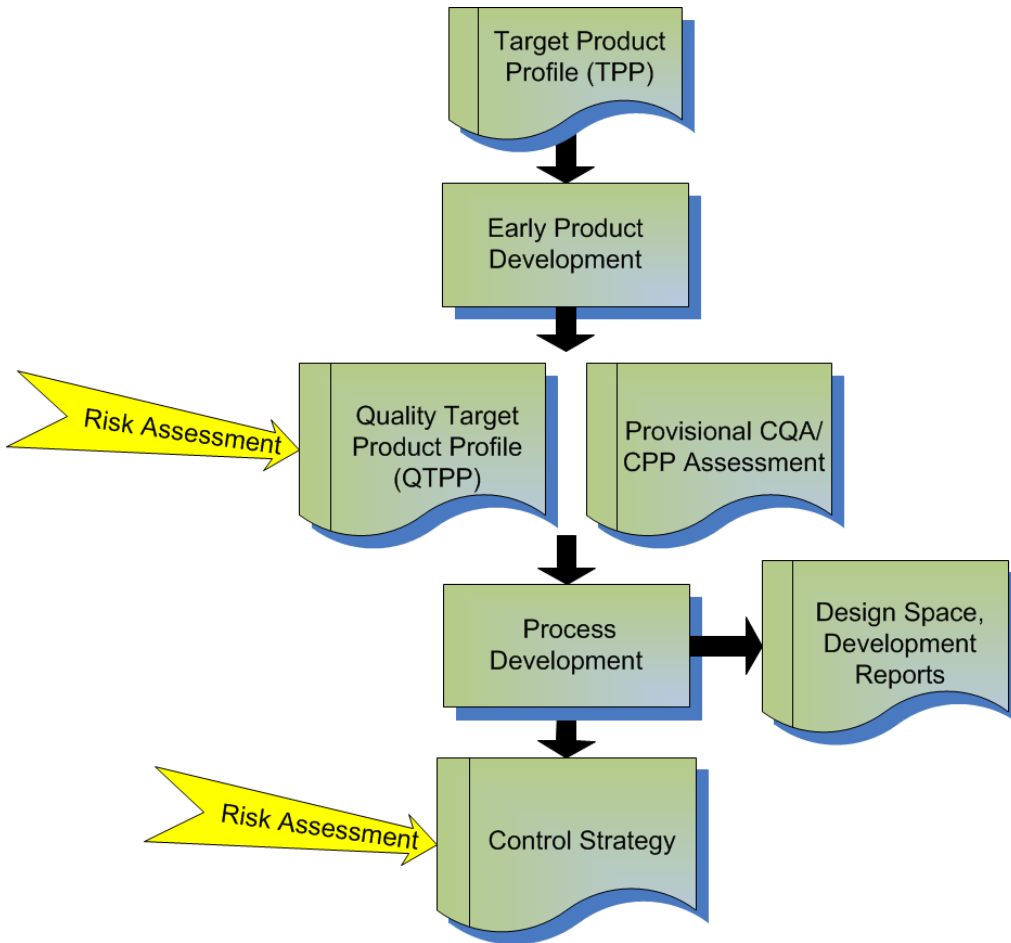Product Development & Manufacturing

TPP

QTPP

Risk Assessment

Design Space

Control Strategy

CPV/Continuous Improvement

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QbD and New Process Development

- The goal of process development is creation of a process control strategy
- Definition of a QTPP, and provisional CQAs and CPPs, is essential to guide development studies
- FMEA and similar tools are very useful for initial CQA and CPP assessments

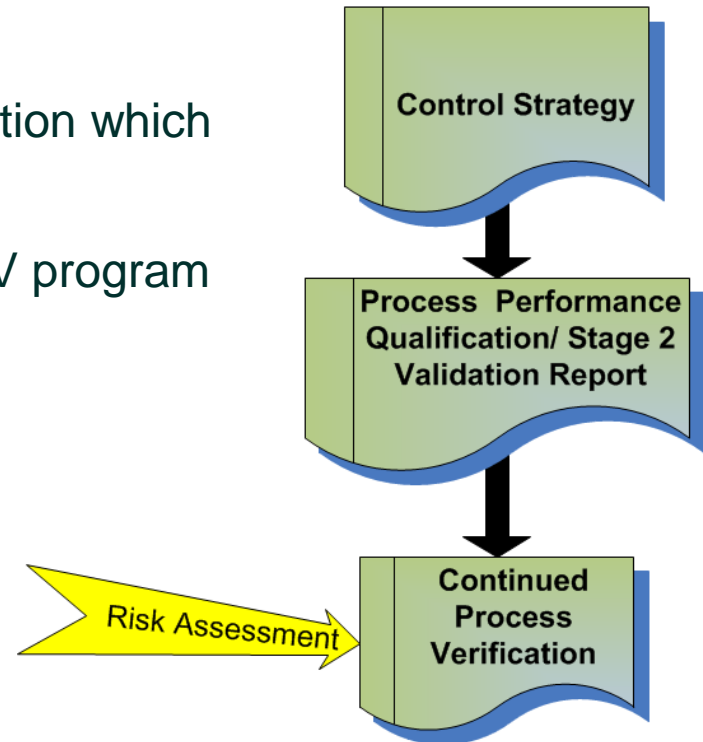Biotherapies for Life™ **CSL Behring**

Applying QbD to Legacy Products

- The minimal requirement for legacy include an established control strategy and process validation which are necessary to create a CPV program.

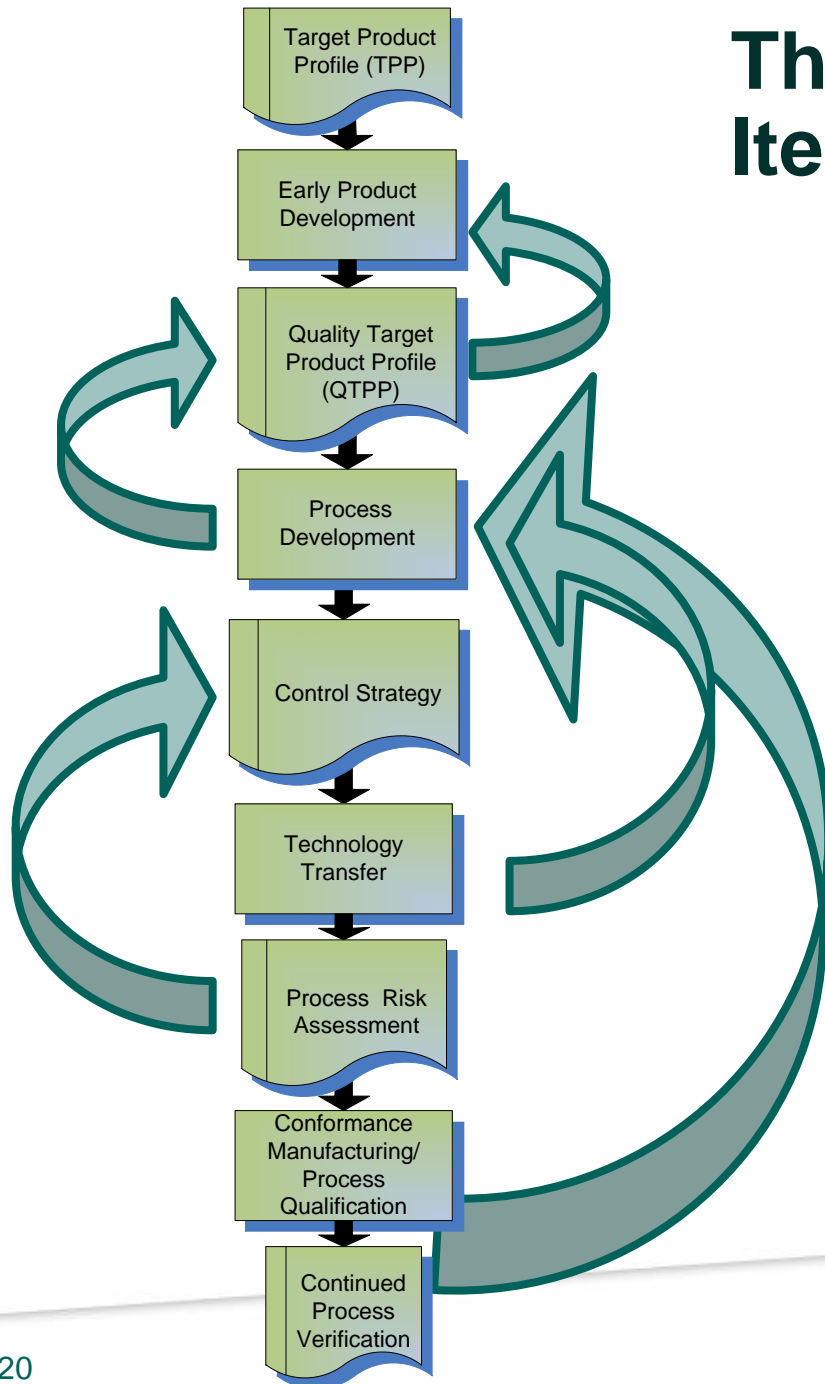- Risk assessment is used in developing the CPV program

From Global Policy:

- *"For legacy products, most of the information required to perform such a risk assessment already exists and just requires compilation.*

- *It is recognized that integration of all legacy products may take substantial time. Each site should prioritize legacy product based on patient impact and create a timeline for evaluation of these products in the QbD program."*

Control Strategy

Process Performance Qualification/ Stage 2 Validation Report

Risk Assessment

Continued Process Verification

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The QbD Process is Iterative

Target Product Profile (TPP)

Early Product Development

Quality Target Product Profile (QTPP)

Process Development

Control Strategy

Technology Transfer

Process Risk Assessment

Conformance Manufacturing/ Process Qualification

Continued Process Verification

- QbD can have multiple feedback modes

- QbD can be applied to any stage of the product lifecycle

- For example, Process Risk Assessment may lead to revision of control strategy

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Conclusions

- Quality by Design is intended to enhance process knowledge and is based on existing guidance and reference documents

- QbD is a quality system that builds on past and sets future regulatory expectations

- QbD can be viewed as a process defined by series of document requirements. These documents organize and demonstrate process knowledge and understanding.

- QbD can be applied to legacy and new products, but the supporting document package may differ.

- The QbD suite of documents are "alive". They can and should be revised as the knowledge base changes.

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Questions?

Broadmeadows T&H R&D Team

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