FDA U.S. FOOD & DRUG ADMINISTRATION

A Regulatory Perspective on Integrated Control Strategy for Therapeutic Proteins

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Overview

- General concepts on control strategies
- Considerations for Control strategy development
  - Pre-licensure
  - Post-licensure

Disclaimer

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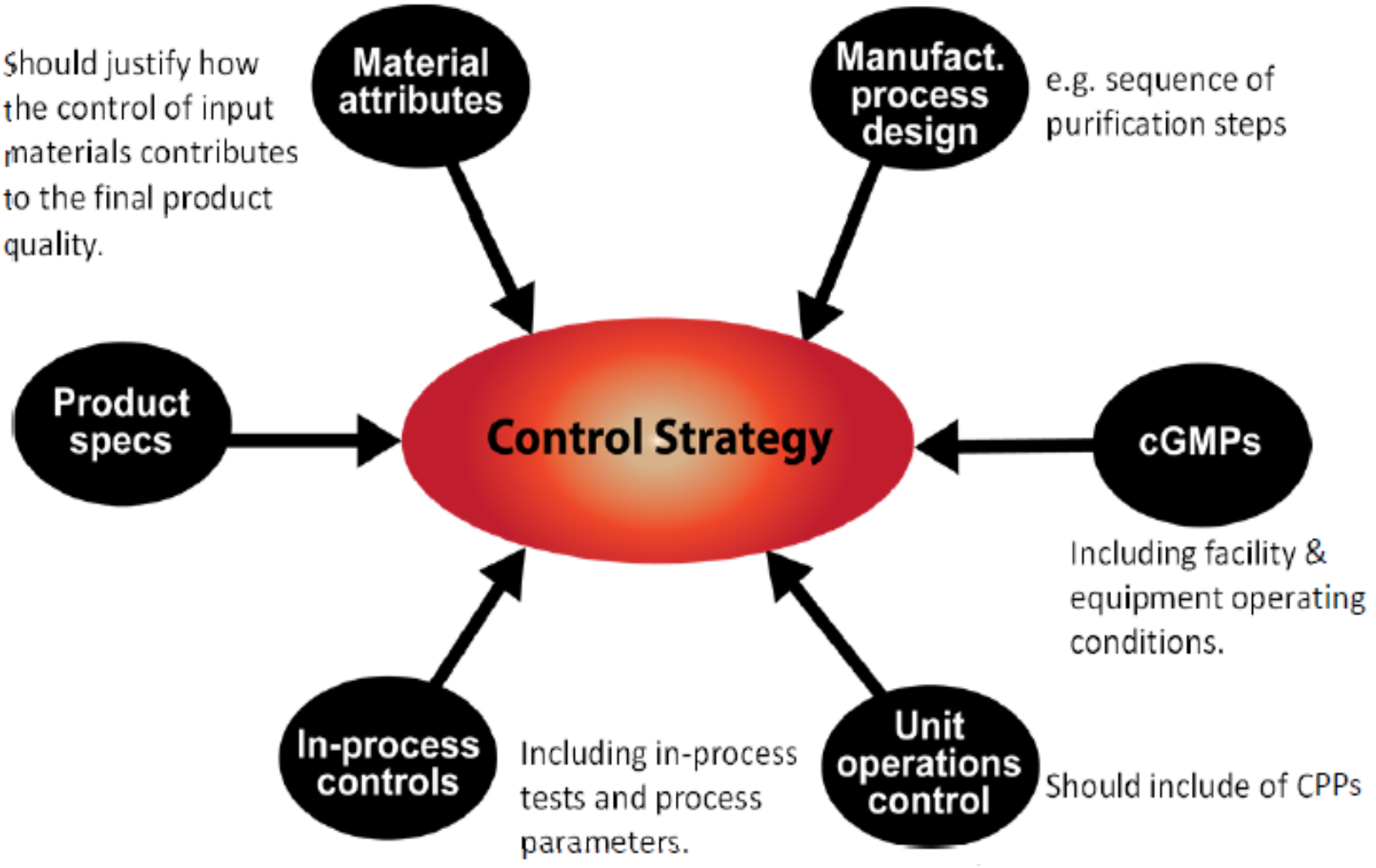
Control Strategy

ICH Q8, Q10 and Q11

- A planned **set of controls** derived from current product and process understanding, that ensures **process performance** and **product quality**.
- Should ensure that each product CQA is within the appropriate range, limit, or distribution to assure product quality.
  - Many of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.
- Designed to ensure that a product of **required quality** will be produced **consistently**.

Control Strategy

Can include but not limited to:



ICH Q10 and Q11

Approaches to Developing a Control Strategy

Traditional

- Set points and operating ranges are typically set narrowly based on observed data to ensure consistency of manufacture.
- More emphasis is placed on assessment of CQAs by end-product testing.
- Based on demonstration of process reproducibility and testing to meet established acceptance criteria.
- Limited flexibility in the operating ranges to address variability.

Enhanced

- Product understanding and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact CQAs.
- Generates better process and product understanding. Sources of variability can be identified in a more systematic way.
- Could be developed through several iterations as the level of process understanding increases during the product lifecycle.
- Provides flexibility in the operating ranges for process parameters to address variability.

A combination of approaches can be used. ICH Q8 and Q10

Considerations for Control strategy development

Pre-licensure

General Considerations for Developing a Control Strategy

- ✓ **Product understanding**
- ✓ **Process understanding**
- ✓ **Capability of analytics**

Quality risk management should be used to establish the control strategy.

- QRM can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.

Control strategy is “Custom made”

- Each product has unique properties that should be understood in order to establish specific manufacturing process, and appropriate in-process controls, controls of input materials, and specifications for drug substance and drug product.

- ICH Q8: “In all cases, the product should be designed to meet patients’ needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission.”

Development of Control Strategy (ICH Q8)

Define QTPP → **Identify CQAs** → **Risk Assessment** → **Design Manufacturing Process**

Quality characteristics of a drug product that ideally will be achieved to ensure quality, taking into account safety and efficacy.

Identify product characteristics that could impact product quality, so they can be controlled.

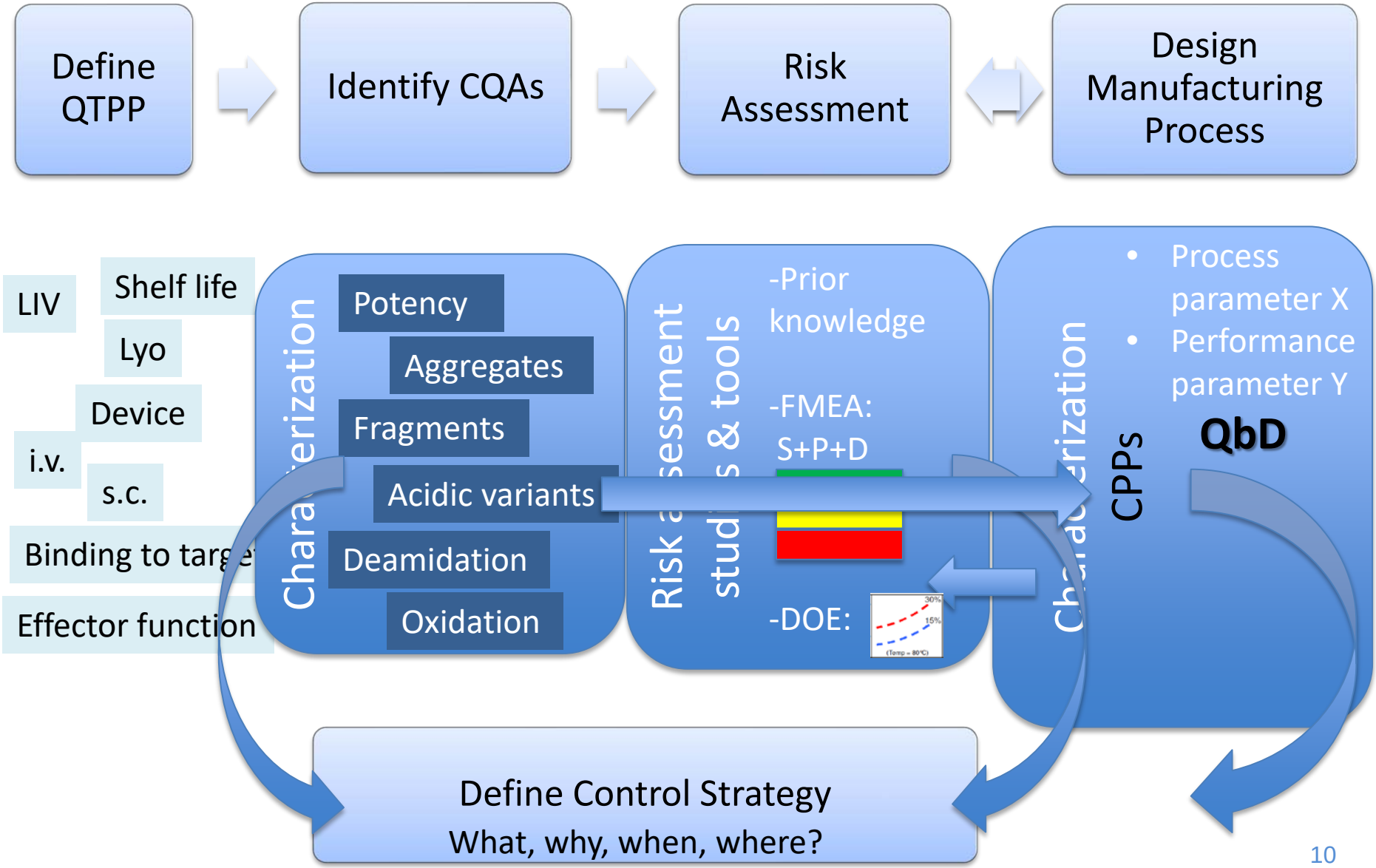
Risk assessment tools can be used to identify and rank parameters with potential to impact product quality based on prior knowledge and experimental data.

Knowledge of CQAs should guide the development of a process that will be consistent with the QTPP and capable to control the QAs.

Define Control Strategy

Based on product and process knowledge.
Derives from management of risk and should lead to assurance of consistent product quality in alignment with the QTPP.

Example: Development of Control Strategy



Changing Landscape of Control Strategies

We have seen use of the following approaches as part of control strategies in INDs or in initial BLAs:

- Extensive prior knowledge to support control strategies (development, process and product quality),
- Process Development and Controls: used QbD approach or specific QbD elements,
- Manufacturing Process: Continuous manufacturing, Single-use systems , etc.
- Analytical testing: Multi-Attribute Methodology, Real Time Release Testing, etc.

Control strategy for Biosimilar products

- Control strategy for a biosimilar product is based on knowledge of the reference product, and pharmaceutical and process development studies for the biosimilar product.
- The process and associated control strategy for a biosimilar product should consistently deliver a product that is highly similar to the reference product.

From "Control Strategy for Biosimilar products: A Regulatory Perspective"
by Gutierrez-Lugo, 2017 PDA Biosimilar Conference

Demonstration of high similarity of proposed biosimilar product to reference product does not guarantee adequate control strategy, i.e., robust and complete control strategy should be in place for marketing of biosimilar product.

Breakthrough therapy products (Accelerated development programs)

- Breakthrough designation is intended to expedite the development and review of drugs for serious or life-threatening conditions with unmet medical need.
- Abbreviated clinical development challenges the CMC development.
- Advanced knowledge → risk benefit evaluations → Expedited CMC development.
- Some activities can be carefully considered at post-marketing.

Accelerated development programs do not change general CMC requirements and expectations of a robust control strategy for marketing approval.

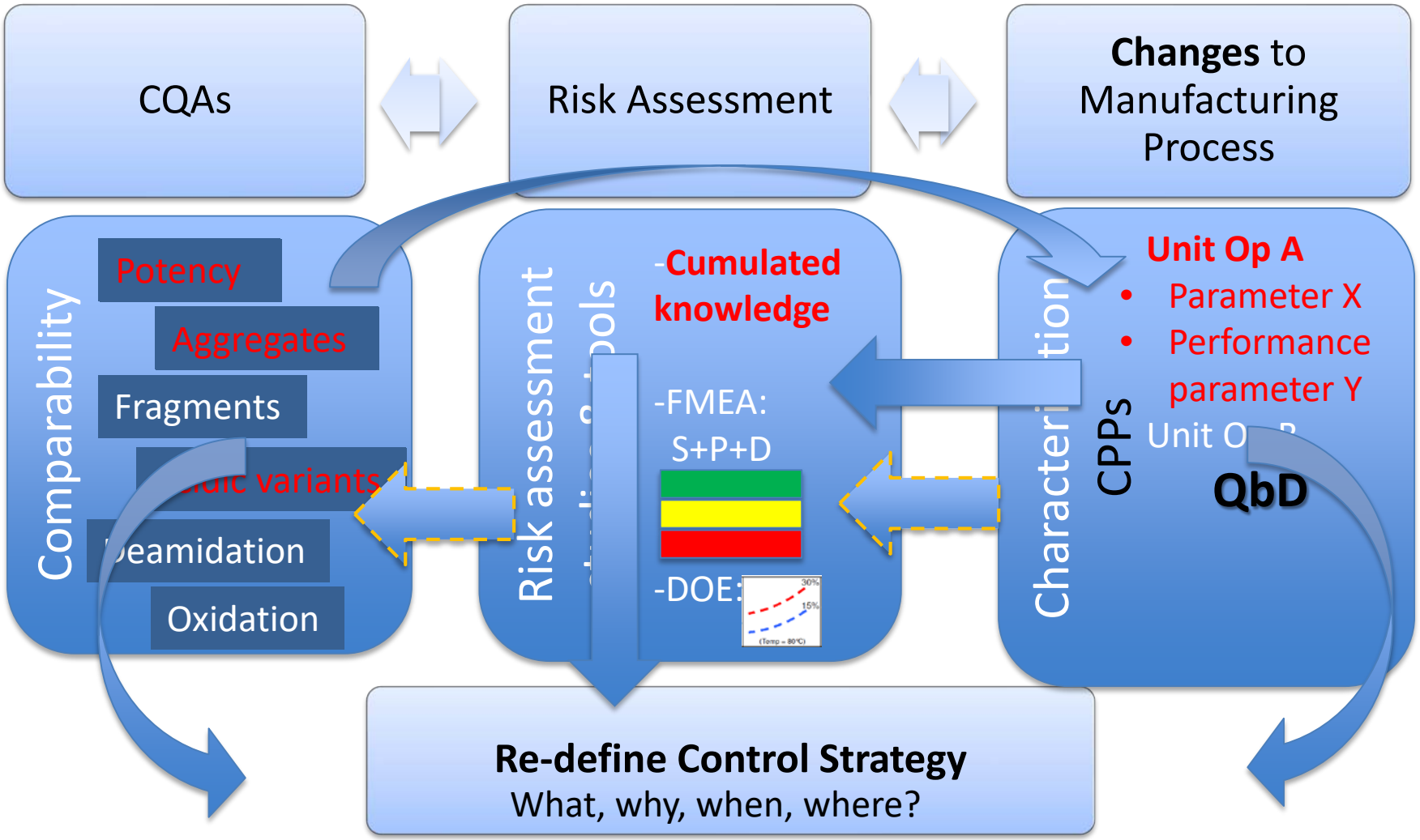
Please discuss the development plans and options with FDA.

Considerations for Control strategy re-development

Post-licensure

Example: Control Strategy for Manufacturing Change

- What parameters to test with process change?



Changing Landscape of Control Strategies

FDA has approved supplements or applications incorporating advanced elements:

- Continued Process Verification,
- Innovative Manufacturing Process: Single-use manufacturing, etc.
- Modification of control strategies for legacy products.

The expectations for control strategies at the time of initial BLA or supplement approvals are changing (based on accumulated process and product knowledge without changing expectation of assurance of quality).

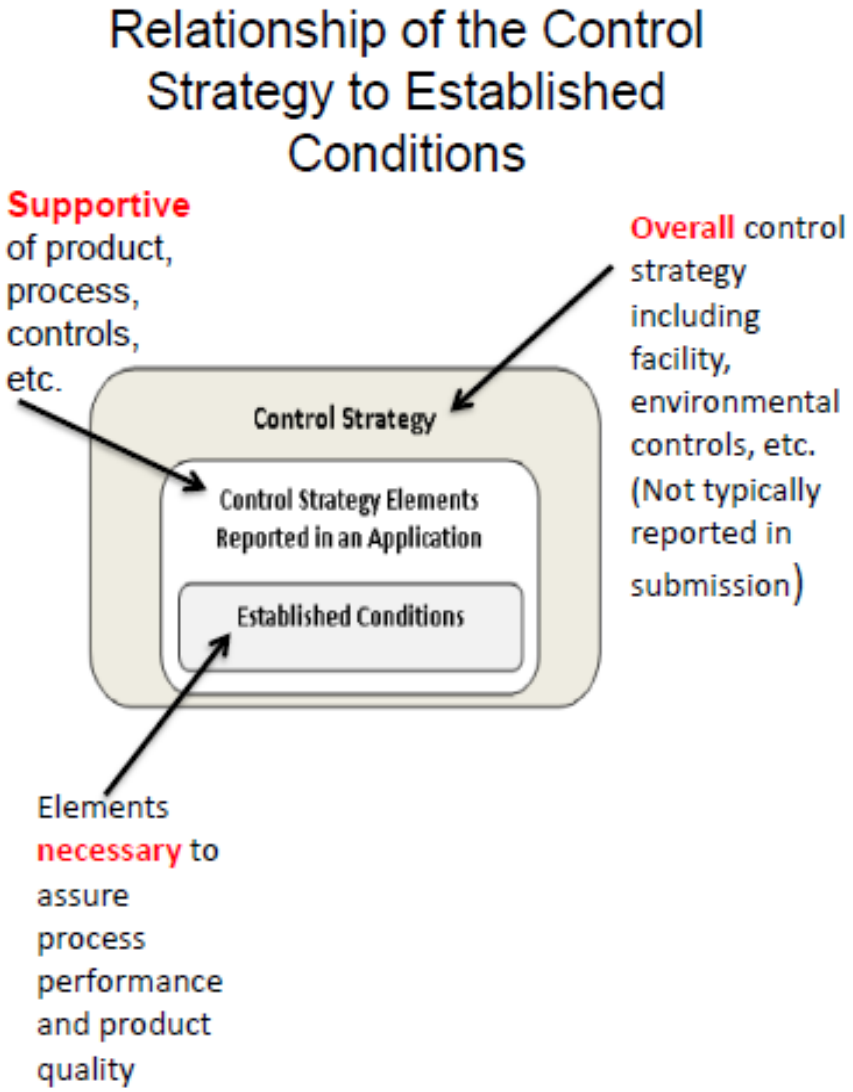
The data and relevant information with adequate evaluation are required to fully support the proposed control strategy.

Control strategy and Established conditions

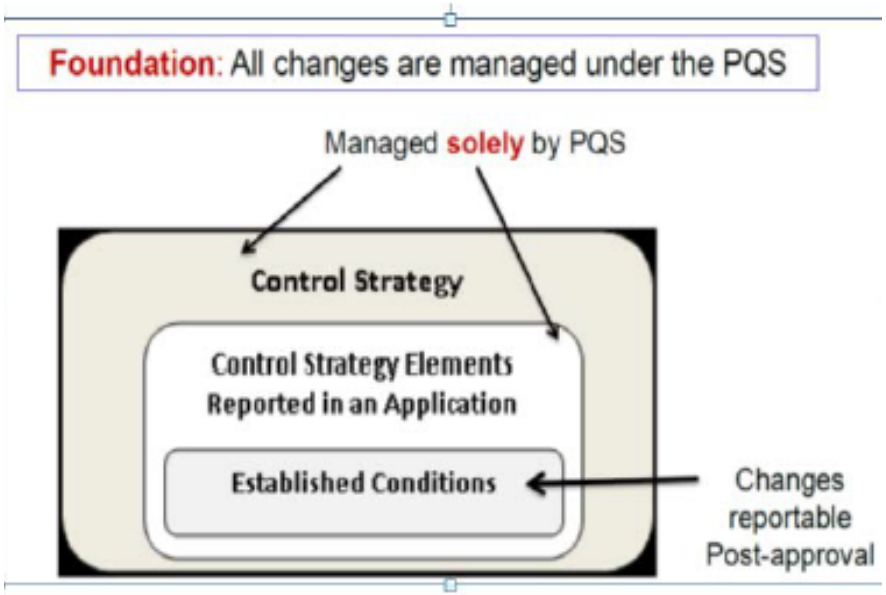
FDA Draft Guidance for Industry: *Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products* (May 2015)

- "The description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure the process performance and quality of an approved product. Changes to the established conditions must be reported to FDA…"
- "…Sufficient detail should be provided in the application regarding the proposed established conditions to assure process performance and quality of the approved product."

Linking Established conditions to Control strategy



All changes whether reportable or not should be managed by the sponsor's quality system



Review of Control Strategy at OBP

- Use development-appropriate control strategy approach.
- Assess the described connections and justifications of the proposed control strategy. Ask: What, why, when, where?
- Utilize tables to assess large data for BLA and supplement reviews:
  - CQA ←→ Risk ←→ Causality ←→ Control strategy (*example)*
  - Manufacturing process development data ←→ Process controls ←→ CQAs

CQA type	CQA	Risk	Origin and process linkage (manufacturing experience)	Control Strategy
Potency	Function of binding to XX (by XXX assay)	Bioactivity, Safety	Intrinsic to the molecule.	DS and DP release and stability testing. XXX
Size-Related Variants	HMWS (by SE-HPLC)	Bioactivity, PK (FcRn), Immunogenicity, Safety	Impact by XXX process. Increase due to XXX exposure and YYY during ZZZ step.	Manufacturing process controls (IPC) at XXX and YYY. DS and DP release and stability testing.

Case example: Control of Fragments

Sponsor's justifications in the submission:

- Fragmented variants are well controlled by the manufacturing process, the historical level is consistently low, and minimal changes are observed on stability under recommended condition. Therefore, rCE-SDS is not included for drug substance lot release or stability testing. …Therefore nrCE-SDS is not included for drug product lot release or stability testing.
- rCE-SDS and nrCE-SDS are performed as IPCs during drug substance manufacturing.

Case example: Control of Fragments

Some questions/potential issues:

- Well controlled by the manufacturing process:
  - How variable will the process be allowed?
  - No development data is provided looking specially at clearance.
- Historical level of fragments is consistently low:
  - Historical *vs.* Future? (Why are we examining DS/DP at release and on stability?)
- Monitored as IPC at the … pool:
  - IPC "action limit" *vs.* Specification acceptance criterion (or IPC "rejection" limit).
  - At which manufacturing step does in-process testing make sense?

Summary

- Control strategies for therapeutic protein products are based on product and process development studies and knowledge:
  - ✓ Generate robust manufacturing process and understanding of product,
  - ✓ Provide understanding of optimal point of controls (possibility to minimize the need for end-product testing).
  - ✓ Identify sources of variability (e.g. from raw materials) and account them in the process parameters and controls.
  - ✓ Provide flexibility of process controls within the studied space.

  Deliver consistent quality, clinical effect, and minimize risk to patient safety.

Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe
- Are efficacious
- Have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed

FDA considers these aspects when evaluating lifecycle management plans and control strategies.

Adapted from Susan Kirshner – CMC Strategy Forum Japan 2015

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