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Process Science to Regulatory Science: Control Strategy and Established Conditions 2019

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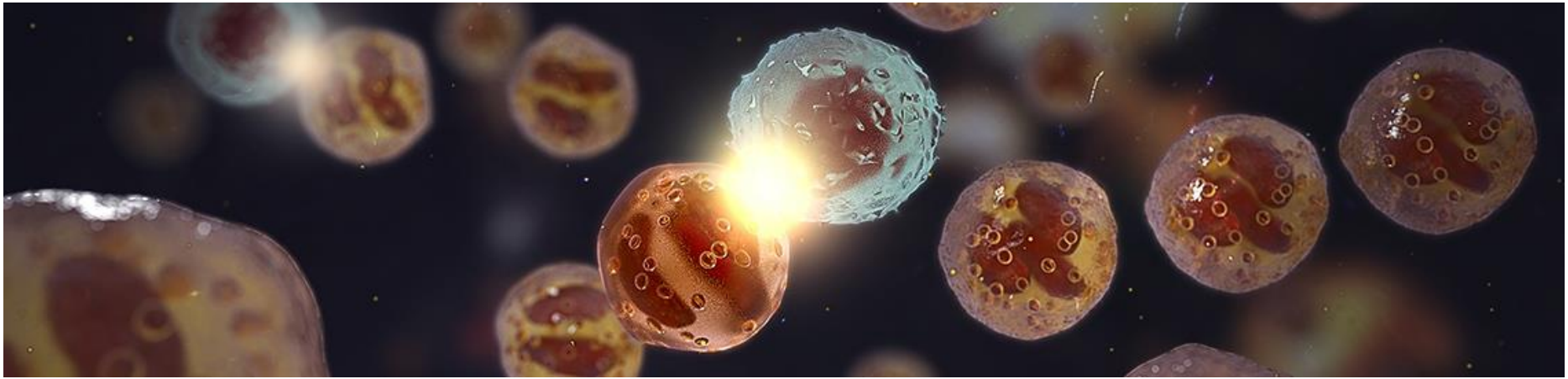


Quality by Design 10 years after

- ICH Q8(R1) approved 2008: first formal ICH definitions of QbD, CQA, CPP
- Now the dominant paradigm for drug development in the biopharmaceutical industry, except……..

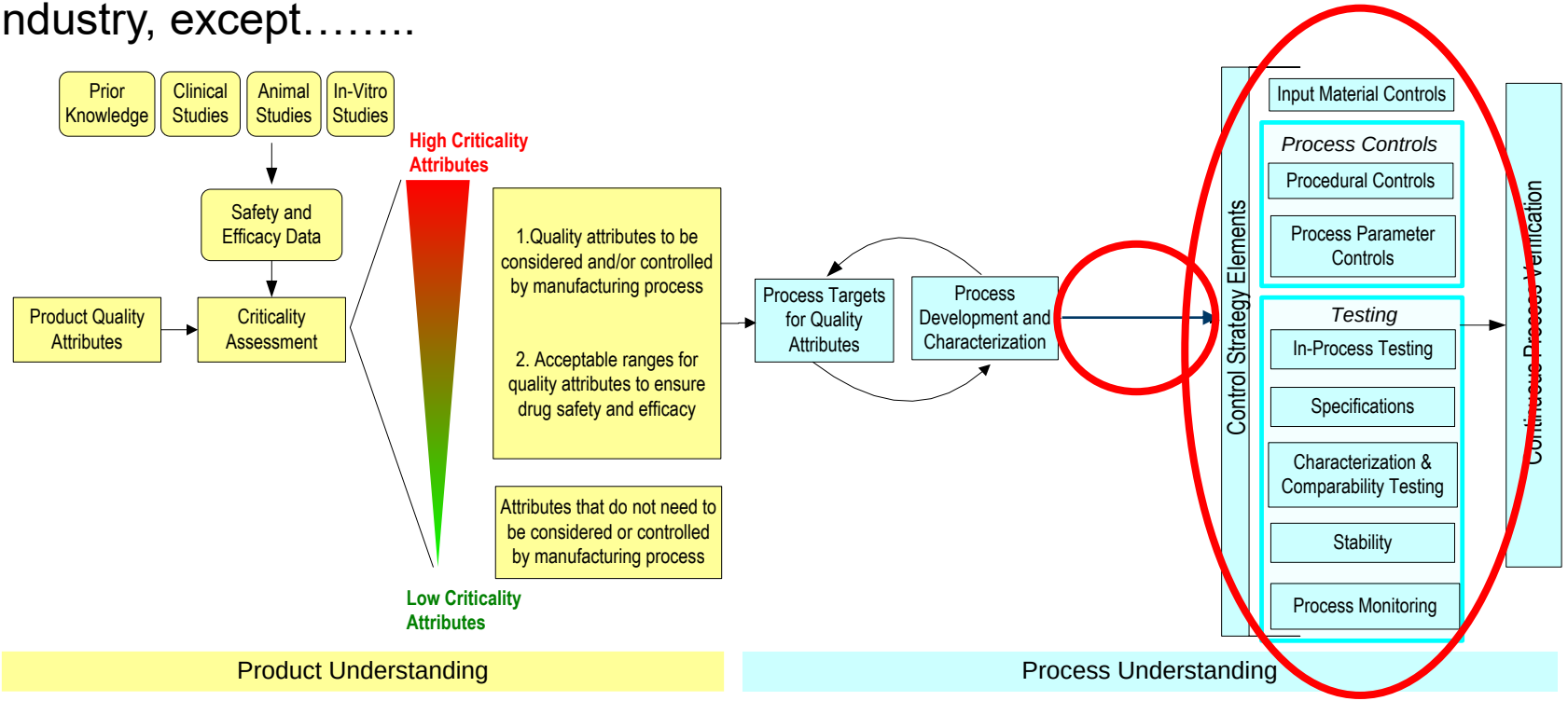
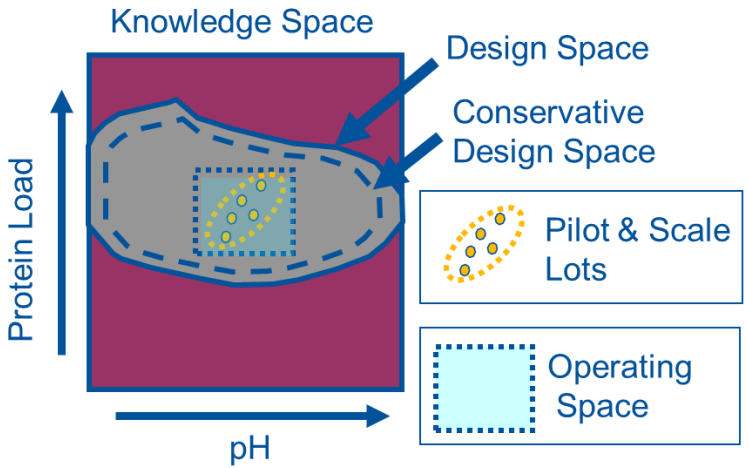


diagram from A-Mab QbD illustrative Case Study (CMC Biotech Working Group, 2009, www.casss.org)

Design Space and the Elusive "Regulatory Relief" of QbD

- "The multidimensional combination and interaction of input variables…and process parameters that have been demonstrated to provide assurance of quality."
- ***Process parameter-centric concept***



- "**Working within the design space is not considered as a change.** Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process."
- ***In practice:***
  - Huge effort required to define and adequately justify Design Space
  - Regulators essentially being asked to pre-approve the universe of possible "movements within Design Space"
  - ***Meaningful regulatory relief seldom realized***
  - **Result: Most companies don't develop or file Design Space**

What is Control Strategy?

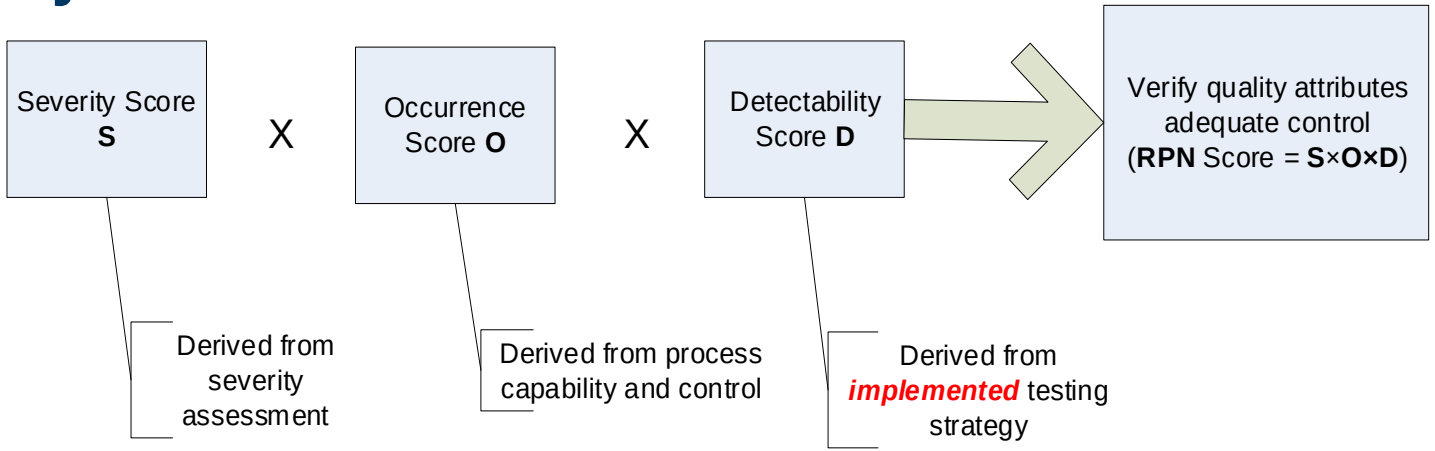
- "A **planned set of controls**, derived from current **product and process understanding**, that **assures** process performance and **product quality**. The controls **can include parameters** and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, **in-process controls**, finished **product specifications**, and the associated methods and frequency of monitoring and control. (ICH Q10)"

- ***Quality attribute-centric concept***

- Has emerged as the most important QbD concept in developing commercial manufacturing processes

- Drives effective justification of manufacturing and quality information in marketing applications and communication with regulators

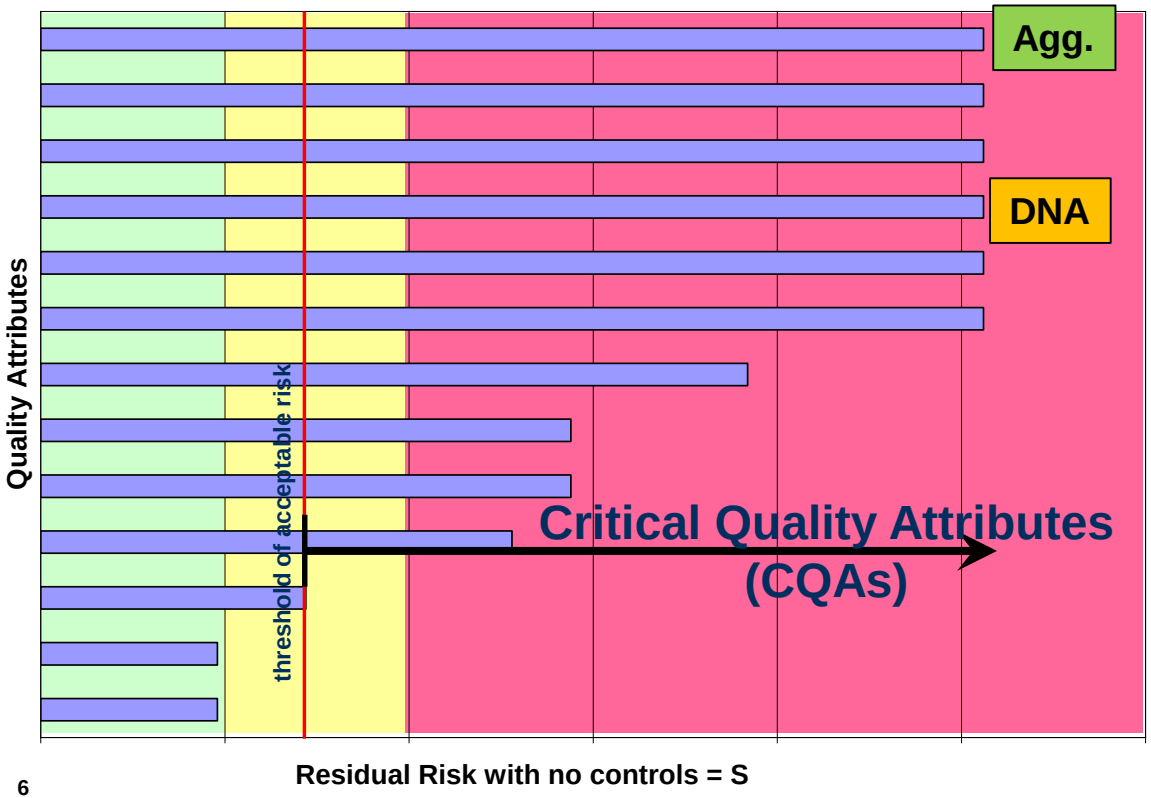
Quality Attribute Risk Assessment via FMEA



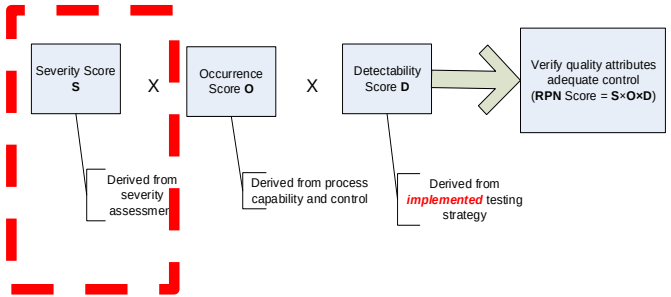
- Risk assess ***each Quality Attribute*** individually
- The combination of the three categories represents the residual risk to the patient arising from each quality attribute
- Objective is to show that manufacturing process and control strategy reduce risk to acceptable levels for ***all*** quality attributes
- Provides a systematic, scientifically based approach to control of quality attributes

Details provided in Schofield, T., Robbins, D., and Miró-Quesada, G. Chapter 21 in: Quality by Design for Biopharmaceutical Drug Product Development (Vol. 18, AAPS). New York, NY: Springer-Verlag New York. 2015, 511-535.

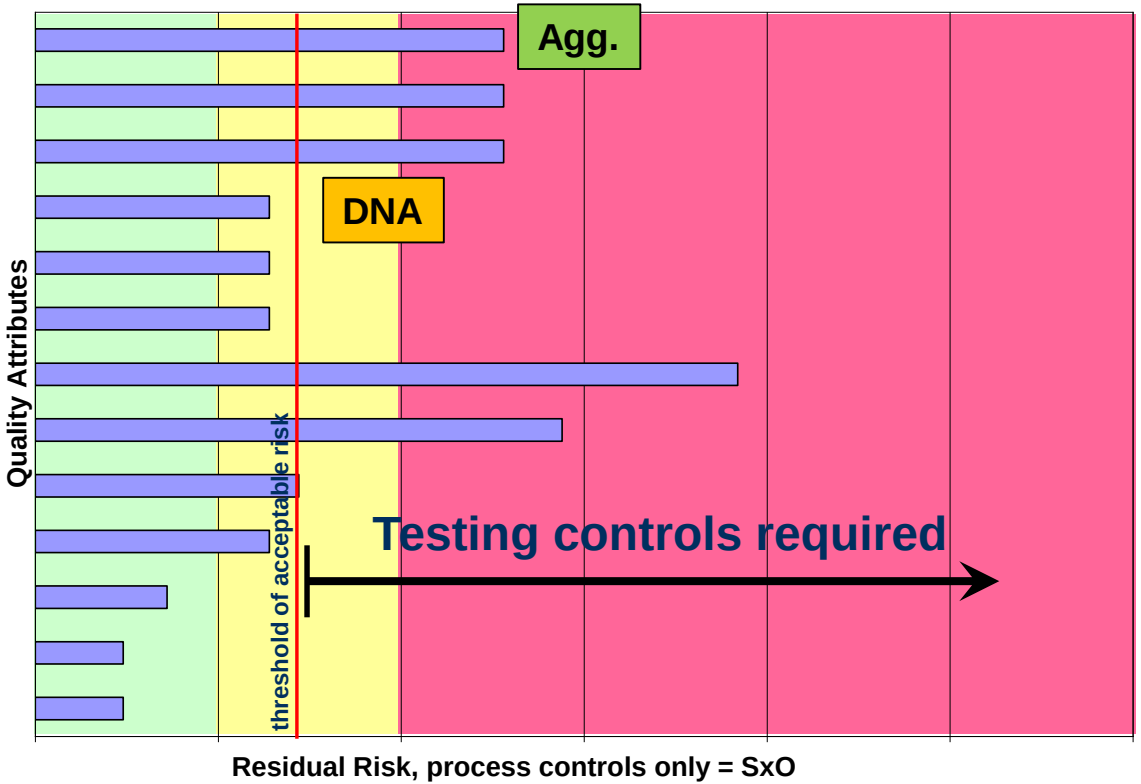
S = Risk to patient if attribute not controlled



Severity (S): Impact on patient's safety and efficacy when dosed with product with quality attribute outside of its appropriate limit, range or distribution

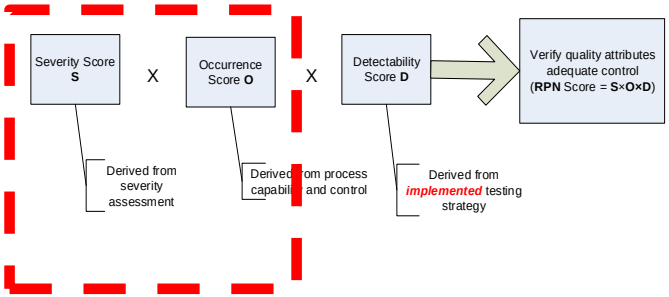


S×O assesses capability of process to mitigate risk to patient (without accounting for testing controls)

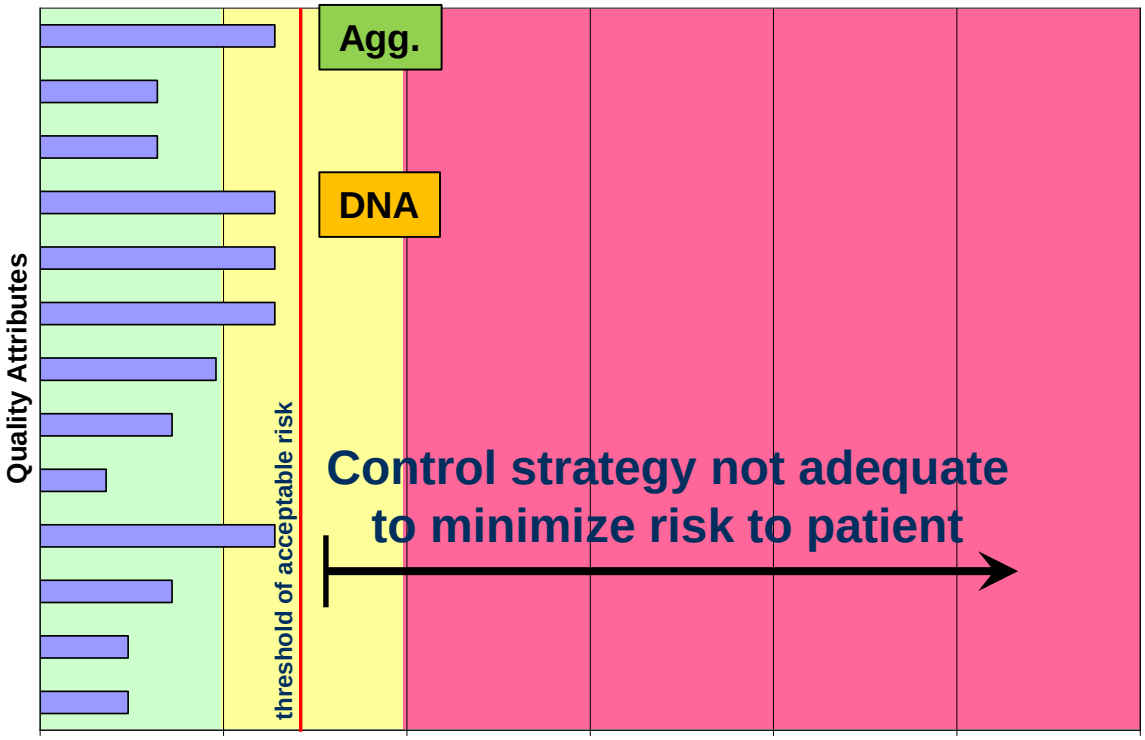


Occurrence (O): Likelihood that a quality attribute will be outside of its appropriate limit, range or distribution

process capability to control attribute

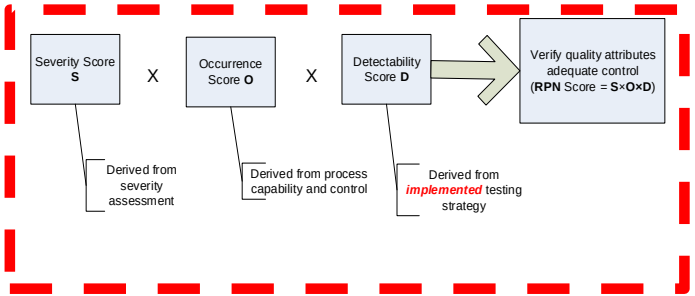


RPN = S×O×D as measure of residual risk



Detectability (D): A measure of the ability to identify whether a quality attribute is outside of its appropriate limit, range or distribution prior to patient dosing

ability of testing controls to detect quality out of range



Control Strategy Example: Host Cell DNA

- **Severity score S is high:** independent of process capability
- **Occurrence score O very low (usually!):**
  - redundancy of multiple robust chromatography steps to clear DNA to very low levels
  - must be justified based on manufacturing experience and process characterization, typically including DNA spiking studies
- **S × O is low:** Residual risk to patient is sufficiently mitigated through process capability and control.
- **Control strategy conclusion:** Process control is adequate ***without routine testing or monitoring***. Tested during process validation to verify control strategy.
- **Lesson learned from FDA review:** Information on upstream variability and excess clearance capability are essential to justifying elimination of release test.

ICH Q12 and Established Conditions (ECs)

- Q12 builds on science and risk-based approaches for drug development outlined in the “QbD” guidelines Q8-Q11

- “CMC changes vary from low to high potential risk with respect to product quality.”

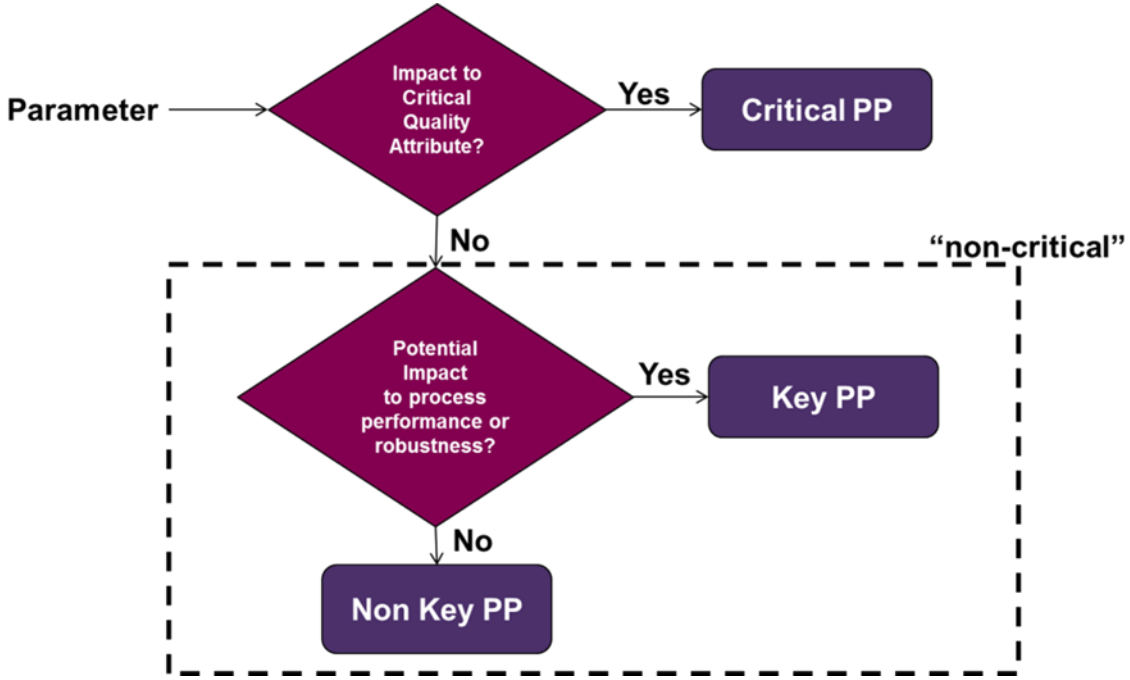
- Definition: “ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.”

- *“Pharmaceutical development activities result in an appropriate **control strategy**, elements of which are considered to be **Established Conditions**.*
  - *All changes to an approved product are managed through a firm’s Pharmaceutical Quality System;*
  - *changes to **ECs** must **also** be reported to the regulatory authority.”*

- **Identification of ECs for the Manufacturing Processes:** *“In addition to the unit operation and the sequence of steps, and in considering the overall control strategy, ECs...should be those inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) that are necessary to assure product quality.”*

ICH guideline Q12: Step 2 draft for public consultation (16 November 2017)

Process Parameter Criticality Assessment (MedImmune/AstraZeneca)



Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8 (R2)).

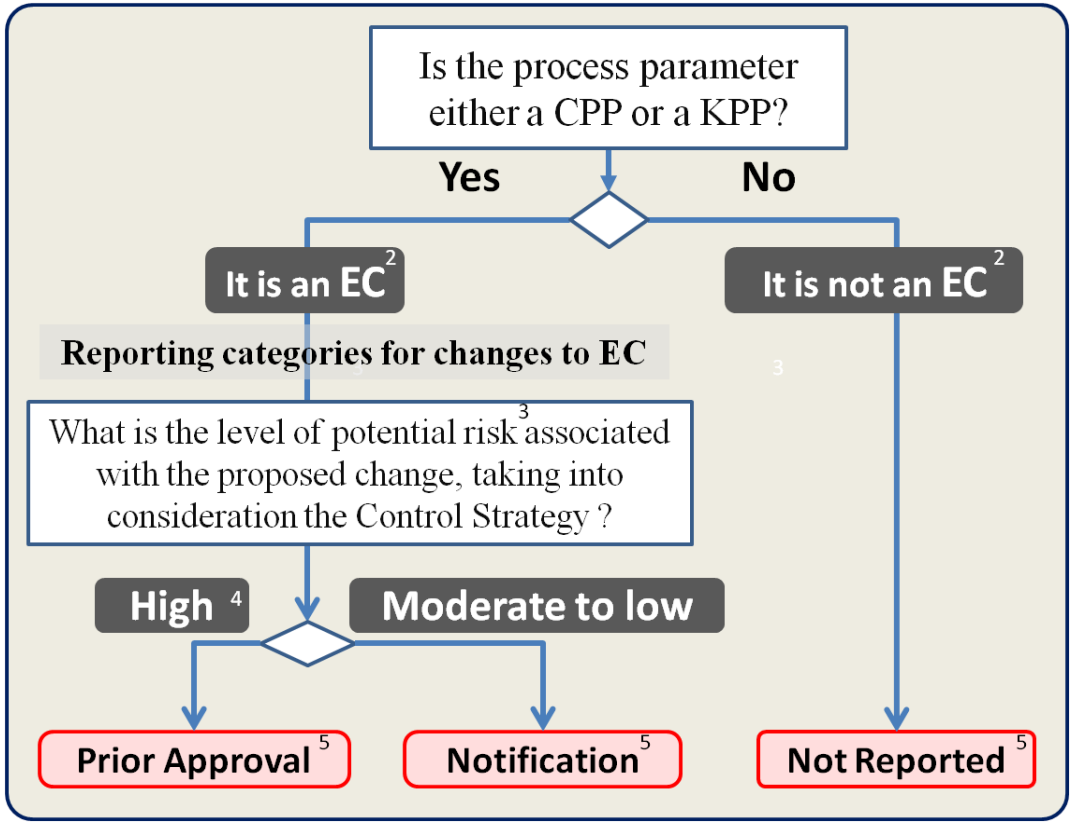
Non-Critical Process Parameter (NCPP): A process parameter whose variability has no practically significant impact on CQAs.

Very small impacts that are well within the acceptable variability for a CQA, based on objective quantitative criteria ("impact ratios"), are not considered to be of practical significance.

Key Process Parameter (KPP): A non-critical process parameter whose variability has an impact on process performance or process consistency and therefore should be monitored or controlled to ensure the process operates consistently as intended.

- Current practice: regulatory submissions designate parameters only as CPP or NCPP.
- KPP designation used only for internal purposes, including selection of parameters for process validation.

ICH Q12: ECs for Manufacturing Processes



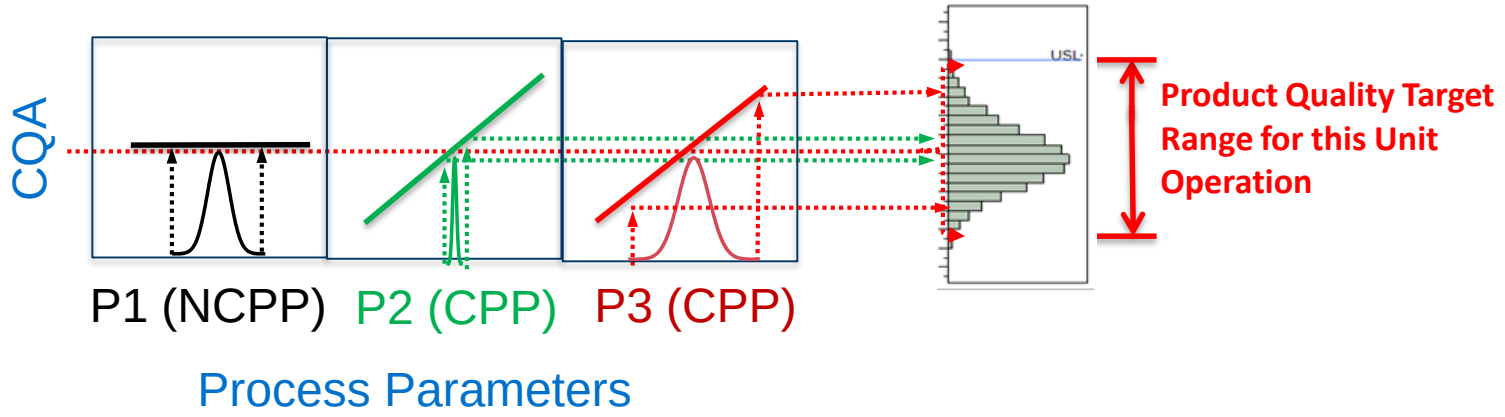
- Development and justification of an effective control strategy and EC identification based on product and process understanding is the key to the regulatory flexibility promised by Q12.
- *"…increased product and process knowledge can contribute to a reduction in the number of regulatory submissions…"*
- CPPs = critical process parameters
- KPPs = key process parameters

ICH guideline Q12: Step 2 draft for public consultation (16 November 2017)

Established Conditions Example: Stability-limiting product variants

Parameters that impact CQAs **and** have a sufficiently wide distribution to realize that impact are likely sources of variability

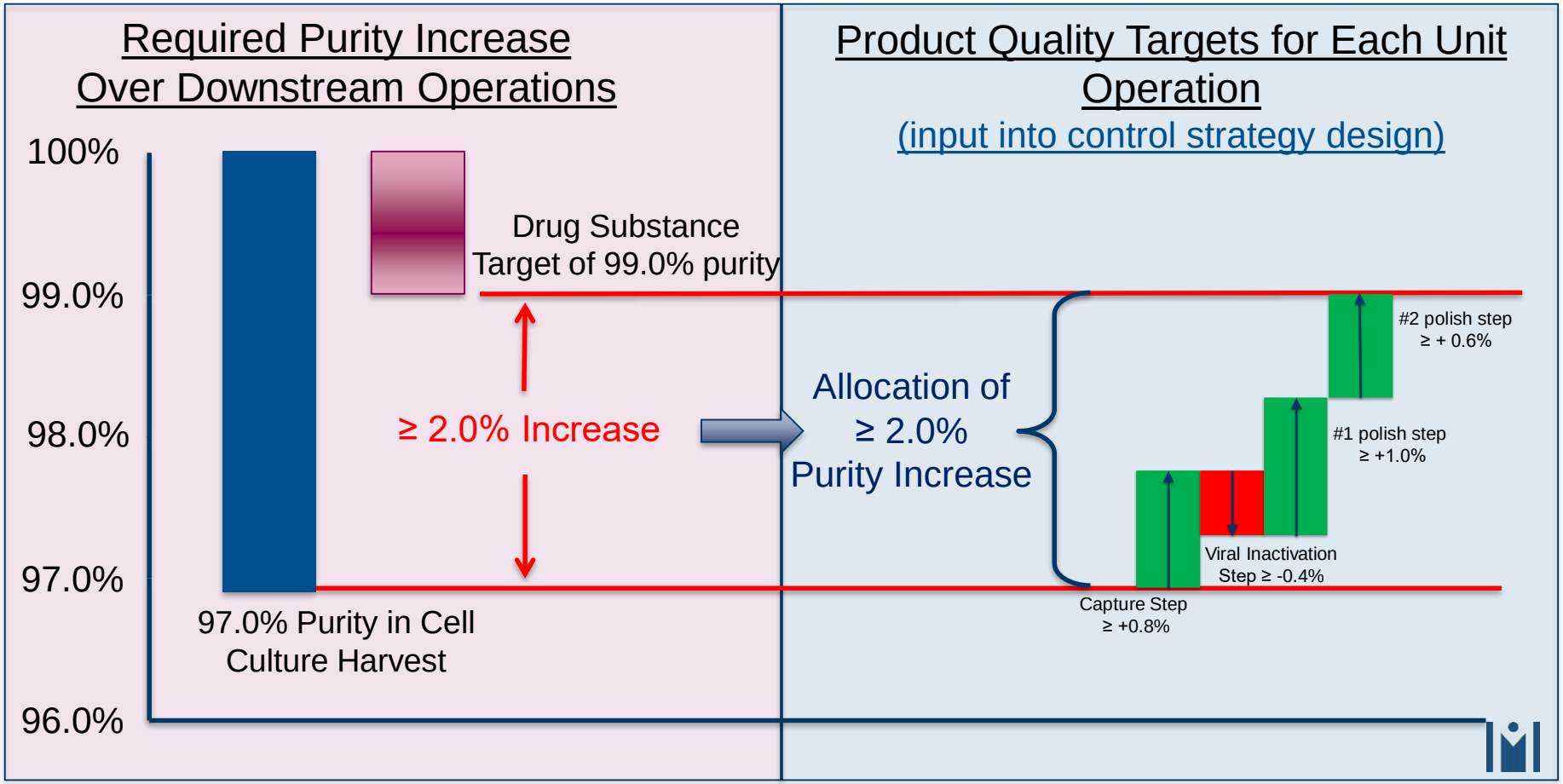
- No impact; distribution narrow or wide (not EC, not reported)
- Some impact but narrow distribution (EC, notification)
- Some impact, wide distribution: Meaningful source of variability (EC, prior approval)



Additional elements of MedImmune control strategy for aggregates and charge variants:

- Formal hold time validation focused on stability-limiting variants (based on development studies)
  - Regulatory feedback challenged hold times on individual site CQAs not in the formal validation
- "Budgeting" of variability between upstream, downstream, in-process holds, drug product mfg. & shelf life
  - Defines intermediate quality targets to guide development and final control strategy

“Budgeting”: Defining Product Quality Target Ranges for Each Unit Operation



How can new approaches improve development and understanding of Control Strategy?

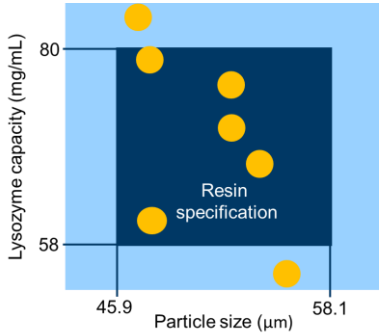
- Improved understanding of ***critical material attributes*** (*e.g.* properties of chromatography resins) and their interactions with process parameters

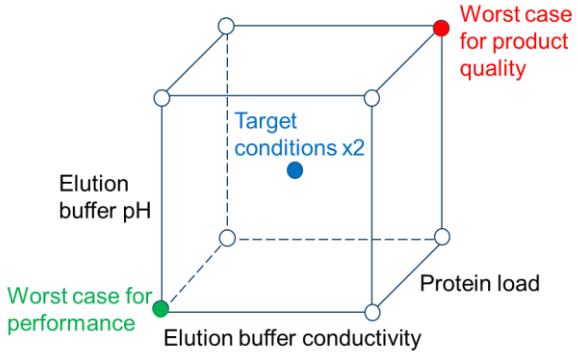
- ***Process characterization approaches*** that provide better understanding of impacts of process parameters and their interactions on product quality attributes
  - High throughput process development
  - Mechanistic modeling

- ***Analytical tools*** for process development and manufacturing controls:
  - Process Analytical Technology (PAT) and real time monitoring
  - Attribute-specific and multi-attribute analyses
    - Separate control strategy for individual charge variant species (already seems to be an expectation)
    - Separate control strategies for individual host cell proteins?

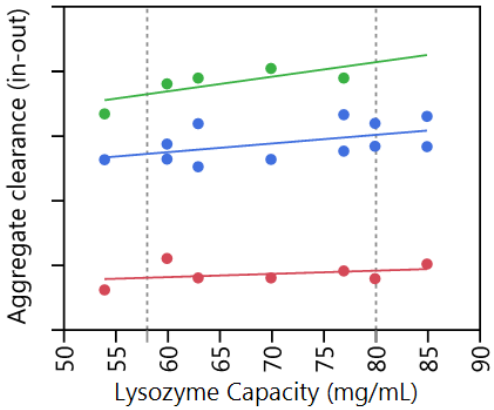
Systematic study of impact of material attributes

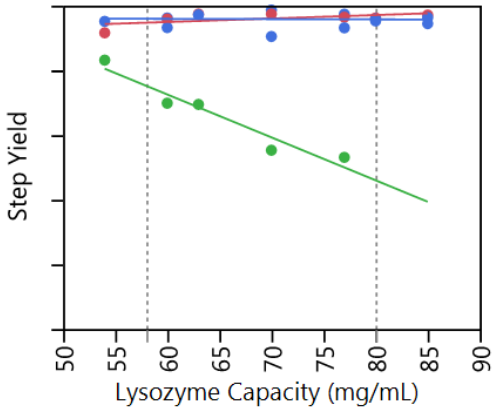
- Control strategy and ECs are intended to include "…attributes related to materials and components…", however these are often neglected in biopharmaceutical development.

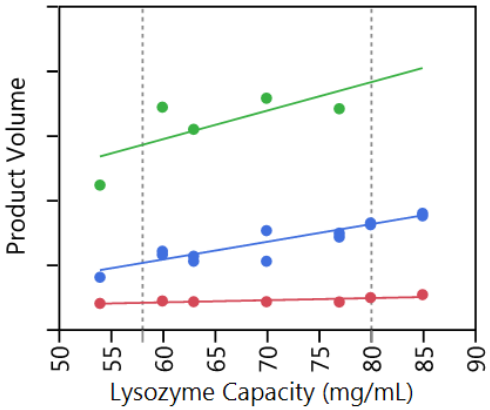




Statistically significant impact of resin variability was observed in interaction with process parameters.







from Hagström *et al.,* "Resin attribute and its interaction with process parameters to impact product quality and process performance for CEX", presentation to ACS National Meeting, April 2017, San Francisco

Process characterization: Can we improve understanding with new tools?

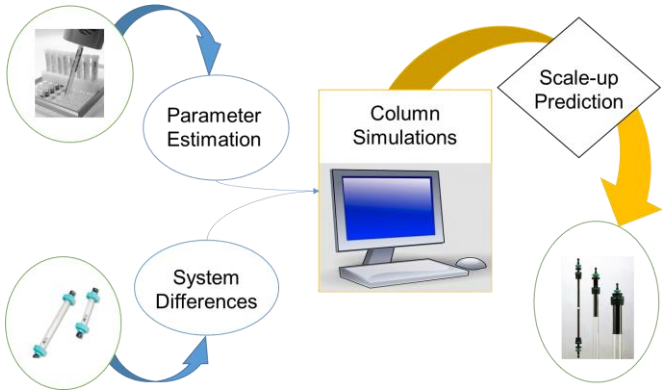
- **Current state:** **Empirical DOEs at bench scale** are the current workhorse to characterize impact of process parameters and their interactions on critical quality attributes.
  - Good predictive scale-down models, efficient for studying interactions
  - Limitations:
    - Heavily resource intensive, even with risk assessments to reduce the number of experiments
    - Difficult to study interactions between parameters in two different process steps
    - No mechanistic understanding; cannot extrapolate relationships

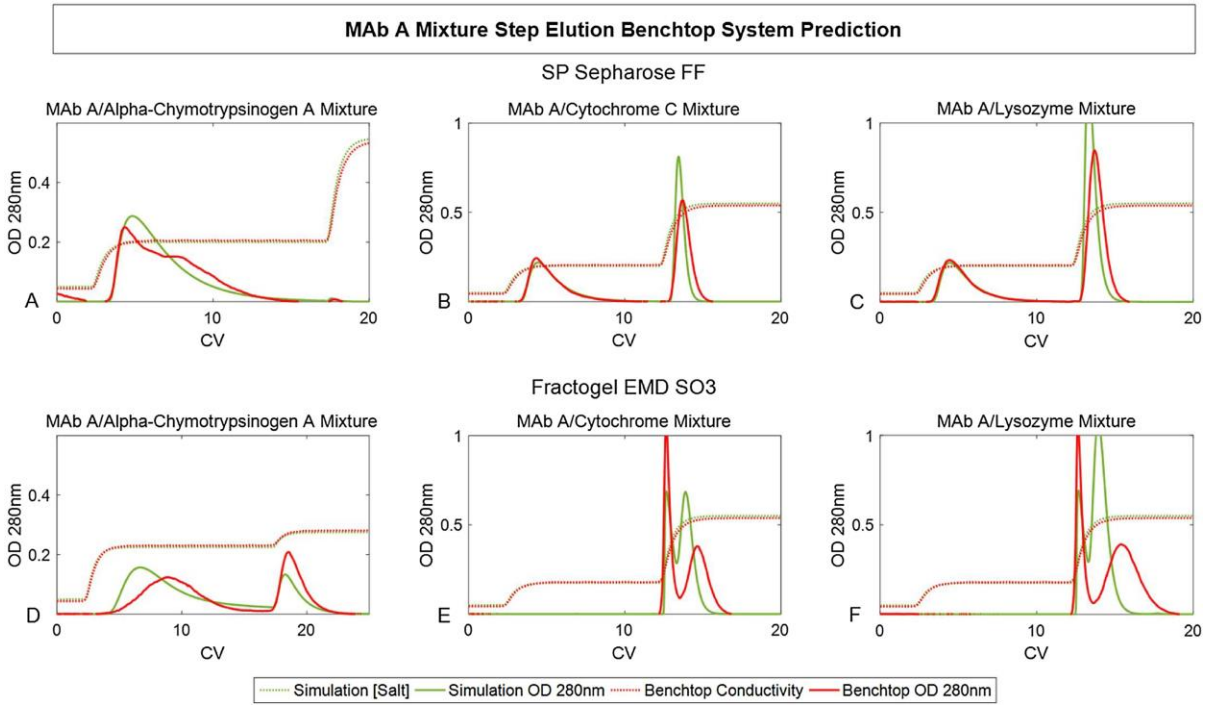
- **New Opportunities:**

  - **High throughput development platforms** *(e.g.*, robotic handling of mini-columns) are increasingly available and provide an opportunity to study more parameters with fewer resources
    - Generally less reliable as predictive models for manufacturing scale (differences in bed heights, column packing, fluid handling)
    - Analytical bottleneck (addressable through automation and PAT approaches)

  - **Mechanistic models** are more available and accessible to the typical user
    - Potential opportunity to improve understanding of impacts
    - Could permit *in silico* simulations to reduce number of experiments
    - Risk of overestimating actual understanding

Can we use mechanistic models to address the predictive deficiencies in high throughput models?





from Keller *et al.*, "Understanding operational system differences for transfer of miniaturized chromatography column data using simulations", Journal of Chromatography A, 1515 (2017) 154-163

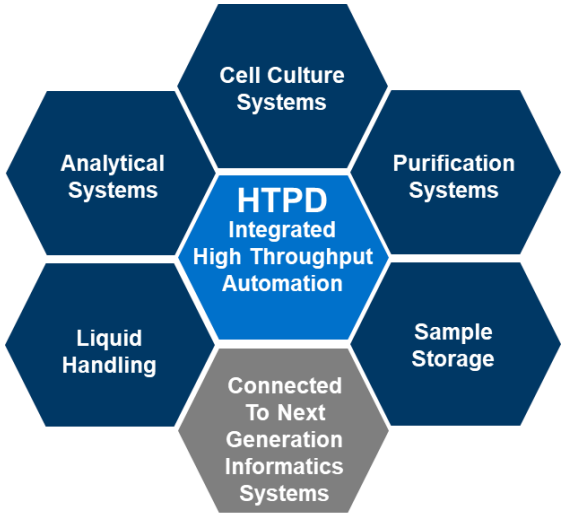
Integrated High Throughput Process Characterization: The Vision

- Automated experiments: Parallel high-throughput process runs with automated variation of process parameters

- Continuous monitoring and data capture of process outputs
  - Incorporate automated analytics (bench-scale “micro-PAT”)
  - Automated on-line analysis and data capture/ export to statistical and/or mechanistic modeling/simulation software

- Incorporate automated linkage of steps in a high-throughput, miniaturized process train

- Ability to better assess linkages between process parameters and indirect effects on quality and process performance in downstream steps



Process Analytical Technology (PAT) and ICH Q12

- "Different approaches can be used…to identify ECs for manufacturing processes:
  - A **parameter based approach**…[non-QbD]…will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
  - An **enhanced approach** [current QbD paradigm] with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs...
  - In certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes)."
    - Example: "manufacturing process steps with in-line continuous monitoring"
    - Potentially useful for continuous manufacturing with adaptive feed-forward/feedback controls

ICH guideline Q12: Step 2 draft for public consultation (16 November 2017)

Conclusions

- Control Strategy, not Design Space, has emerged as the unifying focus of modern drug development and regulatory strategy using the QbD philosophy and tools.
- Risk assessment tools have been developed to ensure and demonstrate that all quality attributes are adequately controlled through process and testing controls to ensure the patient receives safe, efficacious medicine.
- ICH Q12 (draft guidance) emphasizes Control Strategy as the key to identifying established conditions (ECs) and increased flexibility in regulatory pathways for post-approval changes.
- There is much potential for new technologies and tools to increase our level of process and product understanding, as well as the efficiency of acquiring it.

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