ICH Q12 Perspectives: "The Robust PQS"

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- This speech reflects the views of the author and should not be construed to represent the views or policies of FDA or ICH.

Outline

- Desired State
- FDA Draft Guidance: Established Conditions
- PQS Expectations
- Evolution and Emerging Tools
- Conclusion

Desired State

- "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight"
- Most manufacturing changes are managed effectively under the company's Pharmaceutical Quality System (PQS) without the need for regulatory approval prior to implementation
- ICH Q12 can enable this vision by incentivizing
  - Integration of ICH Q8-Q11 throughout the lifecycle
  - True implementation of ICH Q10 principles

FDA Draft Guidance: Established Conditions (EC)

- Description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, **that assure** process performance and quality of an approved product
- **Not all information that is submitted** in an application is an established condition
- The guidance clarifies which elements of the control strategy **submitted in the application** may be considered established conditions

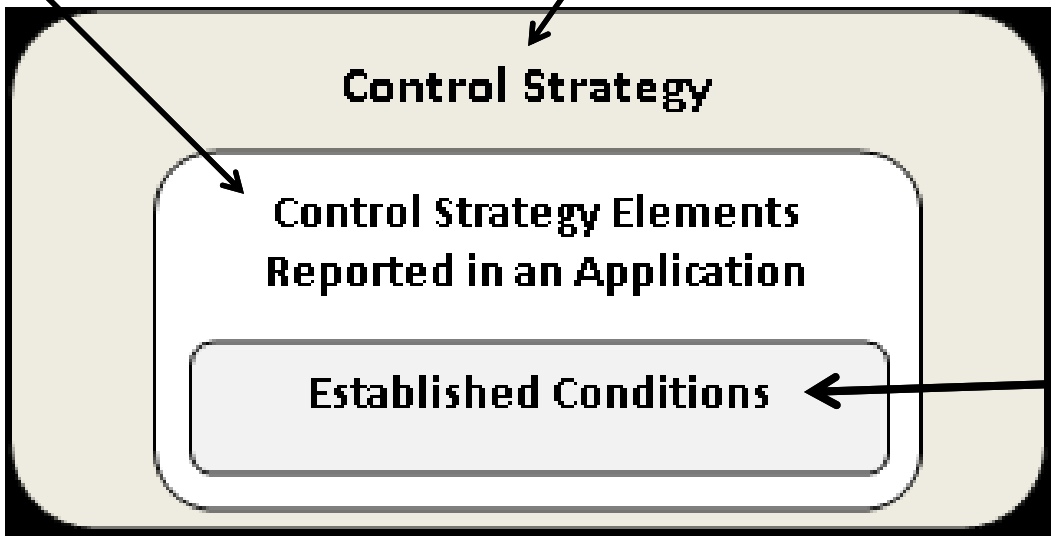
FDA Draft Guidance: Established Conditions (EC)

- Clarification regarding which elements of the CMC information constitute established conditions, **should lead to a better understanding that certain CMC changes can be made solely under the PQS**
- The key to attaining the desired state of Q12 and providing regulators assurance that most changes can be managed by the pharmaceutical industry, without extensive regulatory oversight, is to **provide regulatory authorities assurance that all product quality aspects are managed within a robust PQS over a product's lifecycle**

Linking ECs to Control Strategy

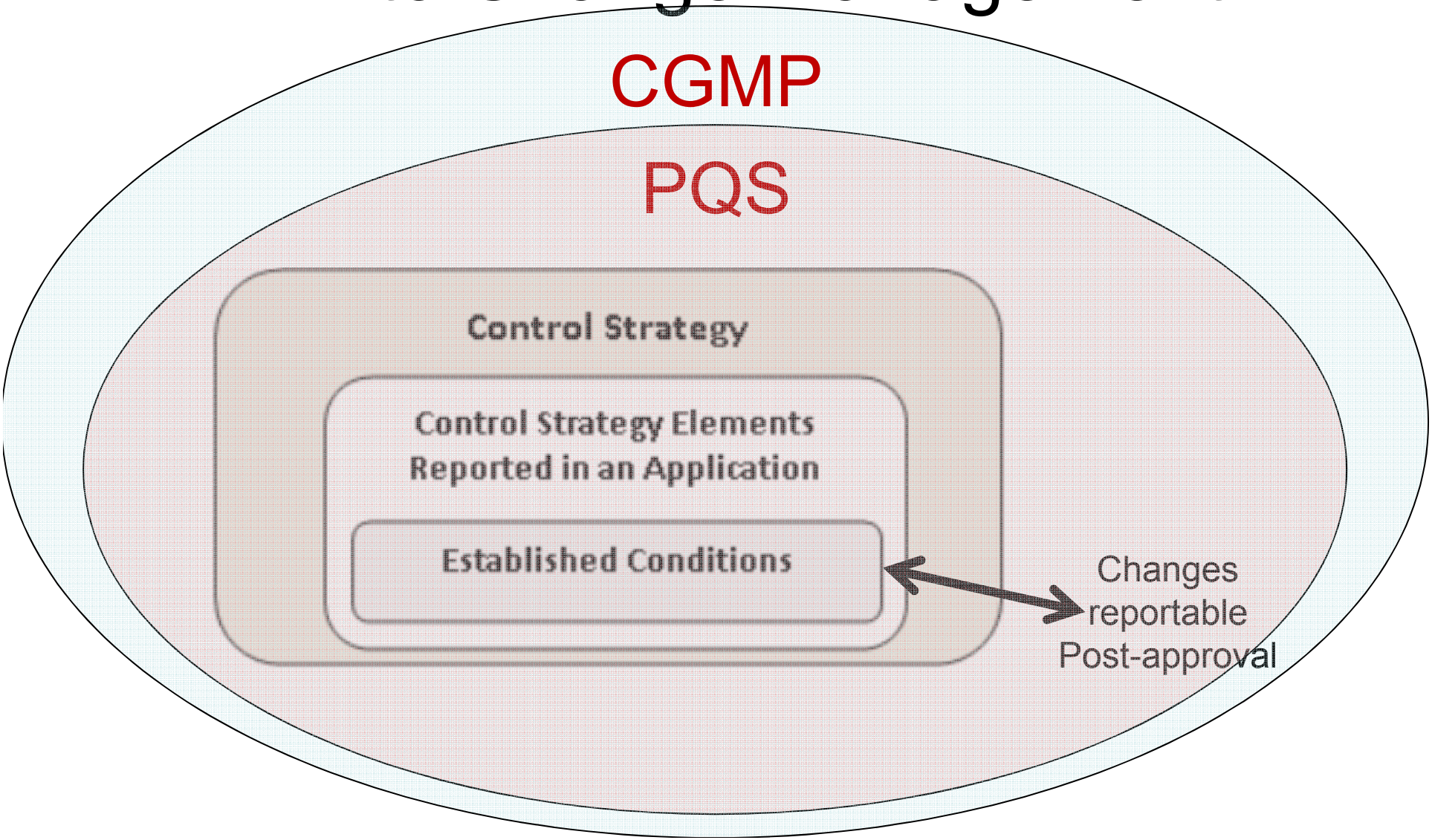
Supportive of product, process, controls, etc.

Overall control strategy including facility, environmental controls, etc. (Not typically reported in submission)



Elements **necessary** to assure process performance and product quality

Link to Change Management



General Site Expectations

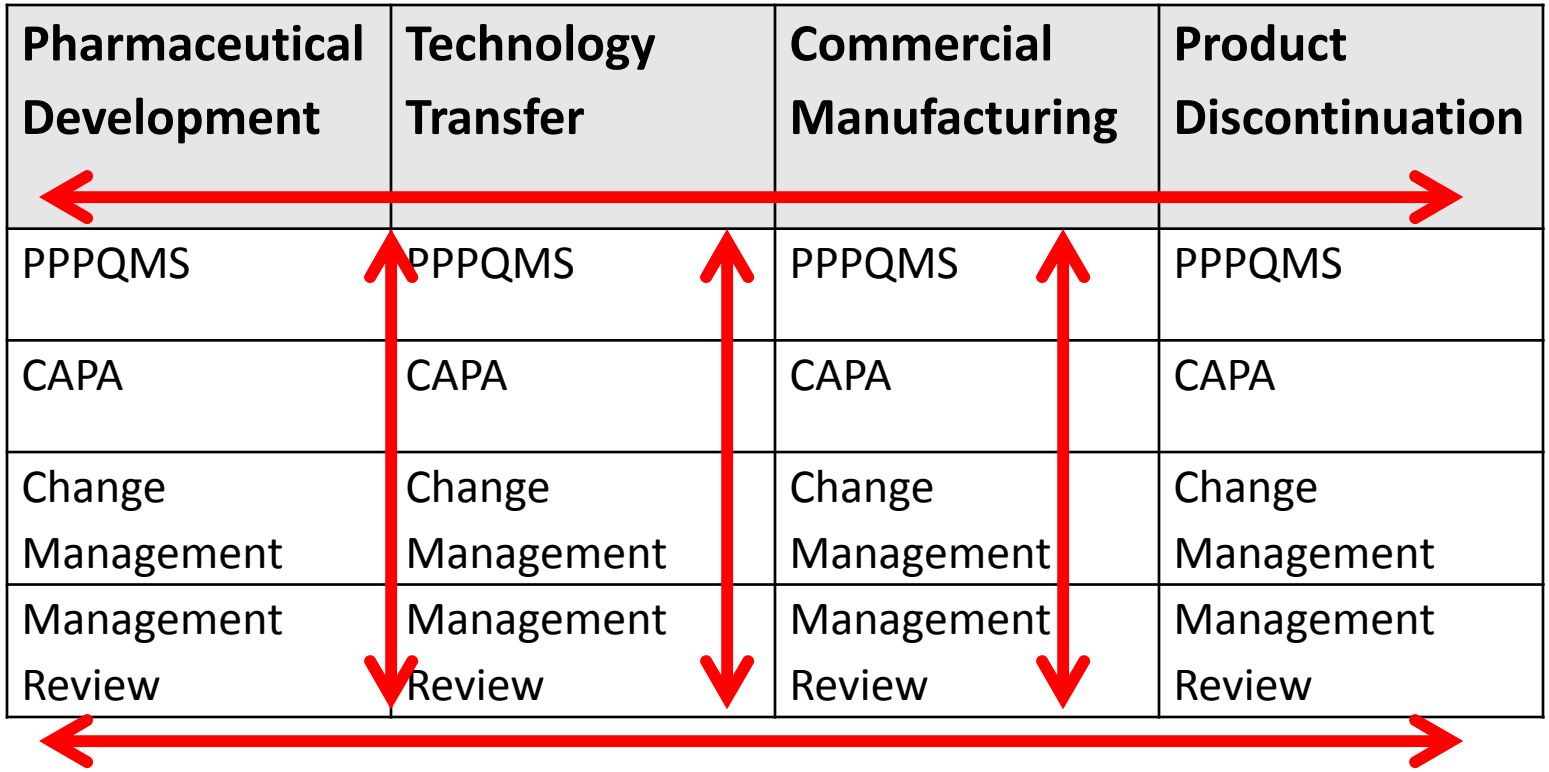
- Sites must operate in conformance with CGMP
- Must have robust manufacturing processes and controls
- Must have adequate governing systems (i.e. six systems)
- CGMP compliant does not always indicate a "robust" PQS
  - i.e. PQS that effectively implements the principles in ICH Q10
- "PQS robustness" - Not a formal FDA term

PQS Expectations

- Process Performance and Product Quality Monitoring System (PPPQMS) utilized over the lifecycle
- Expert teams to drive CAPA and changes
- Formal approach to change management
- Knowledge gained is managed and accessible over the lifecycle
- QRM a foundational driver for the PQS
- Management commitment to quality
  - prioritizes meeting desired quality and patients needs

PQS Expectations

- Complete implementation and multi-dimensional integration across the lifecycle



PQS Expectations

- Why is this so important in the context of ECs?
- Doesn't the strength of the PQS only impact post approval changes?
- Aren't the initial Established Conditions solely dependent on product attributes and process knowledge?

Thought Exercise

- Solid oral dosage form
- Shelf life is proposed to be 24 months at ICH room temperature (RT) conditions
- Stability data across 3 batches shows minimal variability in critical quality attributes (Assay, Impurities, etc…)
- Based on 6 months accelerated, 24 months real time stability data
- Would we agree that the EC for shelf life should be 24 months at ICH RT conditions?

Thought Exercise

- What if an inspection found?
  - Evidence of deleted chromatograms
  - Pattern and practice of trial injections
  - Storage of stability samples in a refrigerator
  - Unreported batches with highly variable or failing results
- Would we agree that the EC for shelf life should be 24 months at ICH RT conditions?

PQS Expectations

- Robustness of the PQS governing the product should:
  - Inform regulators that sound processes were employed in arriving at the initial established conditions
  - Influence the scope and degree of flexibility afforded for post approval changes

PQS Expectations

- Robustness of the PQS governing the product should provide the:
  - **Context** and the **confidence** needed to support the relevance and validity of the established conditions
  - Confidence that lifecycle / post approval changes will be managed appropriately

Enablers to the Vision

- Implementation of a “robust” PQS:
- Common QRM “risk” context
  - Are we talking about the patient, product and process needs?
- Integration of principles across Q8-Q11 across the lifecycle
  - Start with the end in mind i.e. what does your patient need?

Questions Within the Expert Working Group

- Where does the PQS information live?
  - On site?
  - In the application?
  - A little of both?
- How will PQS information be accesses and utilized?
- How will the robustness of the PQS be measured or understood?

Regulatory Evolution: Integration

- Integration between Review and Inspection is essential for a comprehensive quality assessment
- Cannot be ad hoc; has to be a systemic and consistent practice
- Must happen across inspection types throughout product lifecycle
  - Ex. Pre Approval, Post Approval, Surveillance

Regulatory Evolution: Integration

- Basic CGMP compliance <-> robust PQS spectrum
  - 21 CFR 211
  - ICH Q10 principles
- Focus on the “assurance of product quality”
  - relevant knowledge from the application
  - strengths of product and process development
  - substantial concerns related to the manufacturing and/or product quality
- Challenge the effectiveness of the process, control strategy, and readiness to manufacture

Regulatory Evolution: Integration

- Information from review and inspection has to be transformed into knowledge regarding quality
  - Accessible and integrated across the lifecycle
  - Original application, post approval supplements
- Provide confidence that knowledge from sponsor and site were utilized in reaching the proposed ECs
- Commercial knowledge influence on control strategy and ECs
  - ensure that knowledge gained post approval is appropriately utilized to accurately modify ECs

Emerging Regulatory Tools

- Integrated Quality Assessment – Team Based Review
- New Inspection Protocol Project (NIPP)
  - PAI and Surveillance inspections
  - Recognition of positive behaviors in cases where facilities exceed basic compliance
  - Can inform Agency on the robustness of the PQS and Quality Culture during PAI and Surveillance
- Requesting records in advance of inspection
- Quality Metrics

Conclusion

- In order to reach the desired state, the PQS will have to meet the goals of ICH Q10
  - Intentional, active, integrated, throughout the lifecycle, and evident
- Regulators must recognize a “robust” PQS
- Both parties must integrate knowledge across the lifecycle to ensure:
  - Initial ECs were concluded through sound processes
  - Effective post approval control and conformance to EC
  - ECs remain current based on current knowledge