Enabling Improvement through the Product Lifecycle: Change Management within a PQS

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Changes *WILL* happen

- Some things must be changed and there is no option.
  - ✓ Deviations, OOS, batch rejections, customer complaints (reactive change)
  - ✓ Driven as part of CAPA
  - ✓ Supplier stops trading

- Other things can be changed and there is an option.
  - ✓ Continual improvement initiatives (Proactive change)
  - ✓ Due to business or technical reasons
    - o Software upgrade
    - o Product discontinuation

- The PQS must include a robust change management system
  - ✓ Use of Knowledge Management and Quality Risk Management

Change Control: CGMP Requirements

MANUFACTURE

21 CFR 211.100: Any changes in procedures for production and process controls designed to assure identity, strength, quality and purity shall be approved by the appropriate organizational units and reviewed and approved by the quality control unit.

LABORATORY

21 CFR 211.160: Any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

IMPROVEMENT

21 CFR 180: Firm must review, *at least annually*, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.
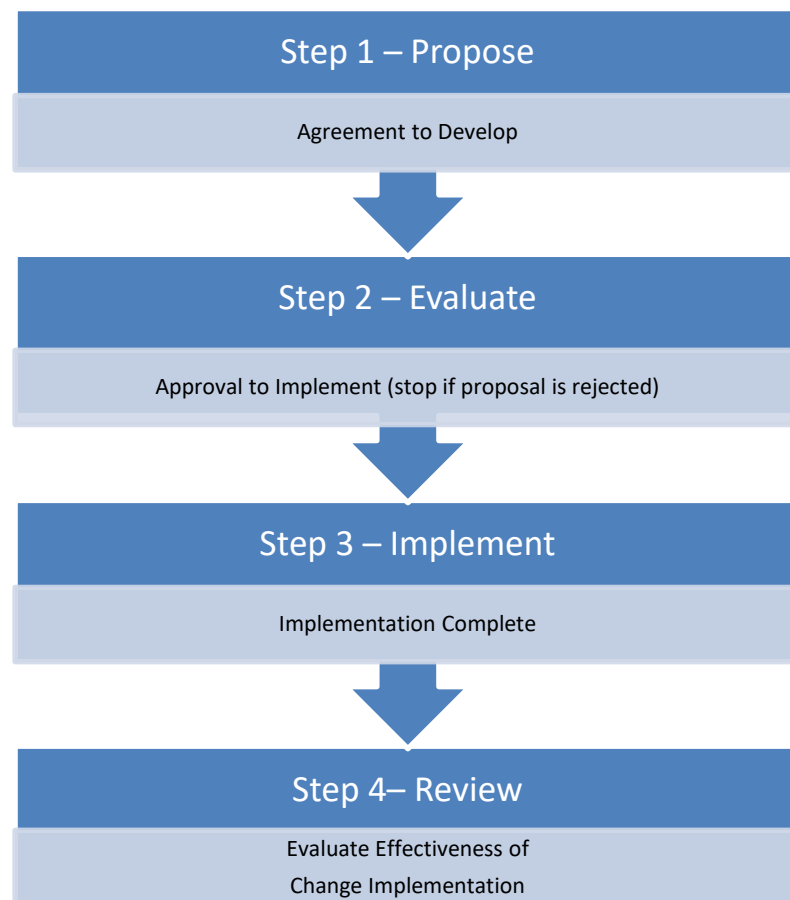
Why is Change important?

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*"Commitment of the company to **control change** to premises, supporting utilities, materials, equipment and processes used in the manufacture of medicinal products is essential to **ensure a continued validation status** of the systems concerned. This commitment should be stated in the relevant company documentation. For example, the Quality Manual, Quality Policy Documents or the Validation Master Plan. As part of its Quality Management System the company should have a defined and formalised Change Control Procedure."*

[PIC/S document PI 006, section 2.6]

Change Management

- **Change Management:** A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)
  - applies across the entire product lifecycle

- **Change Control:** Typically applied to one change at a time

Step 1 – Propose
Agreement to Develop

Step 2 – Evaluate
Approval to Implement (stop if proposal is rejected)

Step 3 – Implement
Implementation Complete

Step 4– Review
Evaluate Effectiveness of Change Implementation

Change Management System (3.2.3)

"The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change."

- ✓ Ensures changes are approved with adequate impact assessment
- ✓ Ensures timely and effective change management
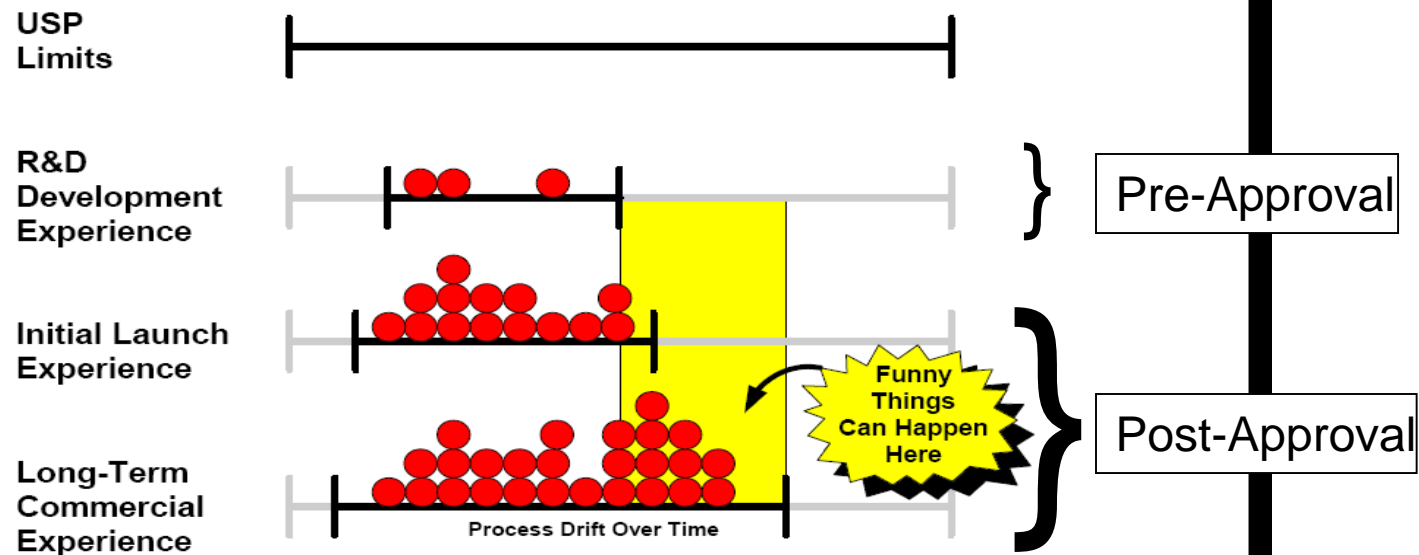
[ICH Q10]

Change Management System (3.2.3) (c)

Proposed changes should be evaluated by <u>expert teams contributing the appropriate expertise</u> and knowledge from relevant areas…to ensure the change is technically justified.

✓Ensures changes are approved by right personnel

[ICH Q10]

Why Processes Need to be Re-evaluated Throughout a Product Lifecycle

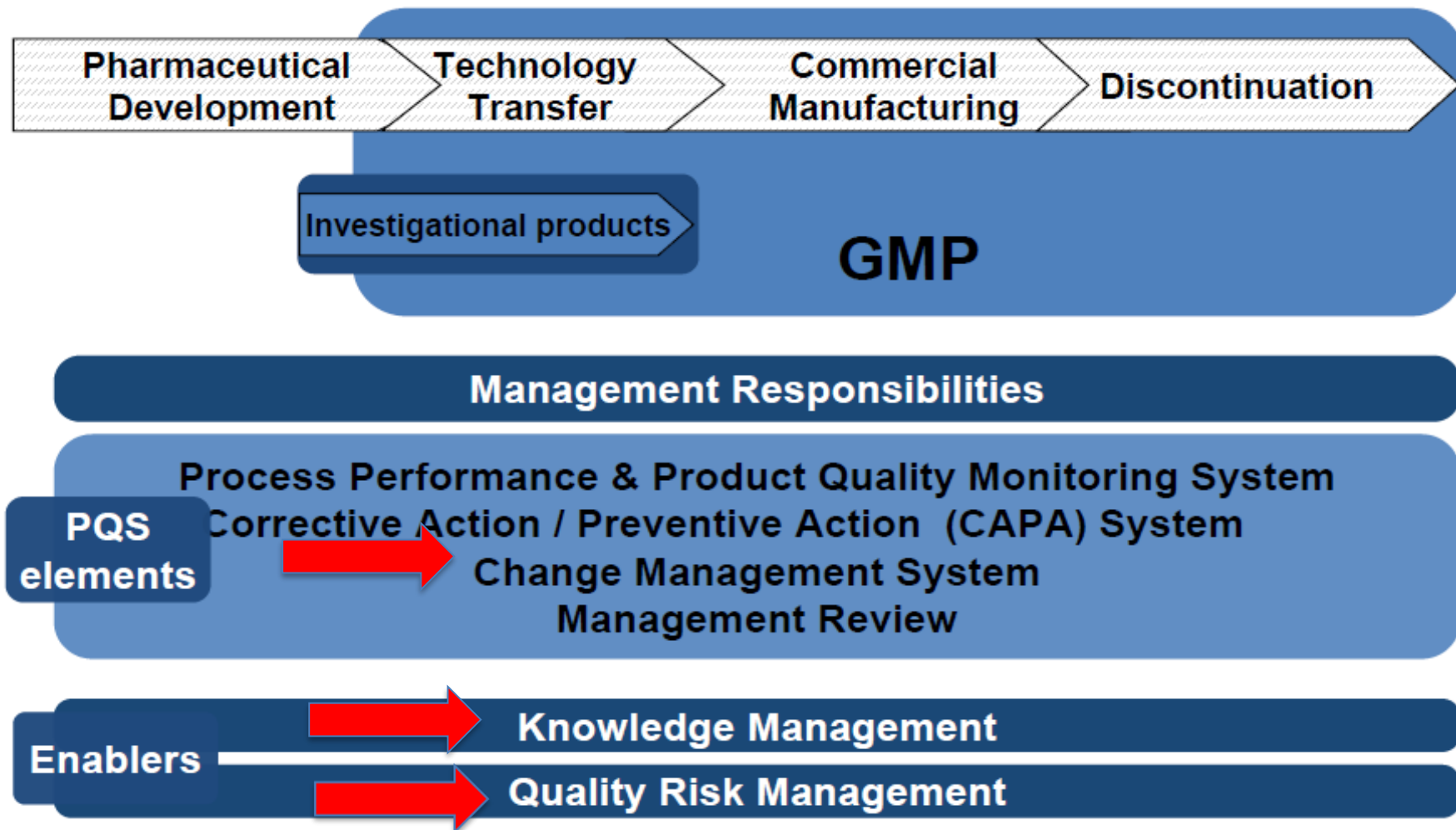Raw Materials: Typical Historical Experience with Physicochemical Properties

USP Limits

R&D Development Experience — Pre-Approval

Initial Launch Experience

Long-Term Commercial Experience — Post-Approval

Funny Things Can Happen Here

Process Drift Over Time

Innovation in Pharmaceutical Development and Manufacturing - Why? May 2007   34   © 2007 TAP

Change Management Drives Continual Improvement

- Proactive usage of knowledge…not reacting to problems
- Continual improvement is part of the company culture… Change is seen as something good!
- Process changes are controlled via a robust change management system
  - Proactively driven by outputs from monitoring / trending / improvement / innovation
  - Use expert teams and knowledge to evaluate and set success criteria
  - Use QRM commensurate with level of risk
- Process control change is verified as successful (or not)
- Undertake in timely and effective way and track

ICH Q10 Pharmaceutical Quality System

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Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Discontinuation

Investigational products

GMP

Management Responsibilities

PQS elements
- Process Performance & Product Quality Monitoring System
- Corrective Action / Preventive Action (CAPA) System
- Change Management System
- Management Review

Enablers
- Knowledge Management
- Quality Risk Management

Knowledge Management

- Systematic and lifecycle approach to acquiring, analyzing, storing and disseminating knowledge on products, processes, components…

- Provides the basis for science and risk-based approaches in the PQS
  - Product and process development
  - Manufacturing
  - Change management
  - Continual improvement

Building Knowledge... starts in Pharmaceutical Development

"However, the knowledge and science-based discussion included within Pharmaceutical Development is intended to be applicable over the lifecycle of the product and may need to be updated as new information on the manufacturing science and technology become available."

[Final Concept Paper Q8: Pharmaceutical Development]

Building Knowledge Throughout the Lifecycle...Drives Change Management

Table III: Application of Change Management System Throughout the Product Lifecycle

| Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science- and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

[ICH Q10]

Building Knowledge…Driving Change

"*Monitoring during* **scale-up** *activities*

can provide a **preliminary indication of process performance** *and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in* **further developing** *the control strategy.*"

[ICH Q10 – Technology Transfer]

Building Knowledge… Continued Process Verification

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- – Process performance and product quality monitoring systems (PPPQMS)

- – Management review

- – Corrective action & preventive action (CAPA)

- – Change Management

Pre-approval

Post-approval
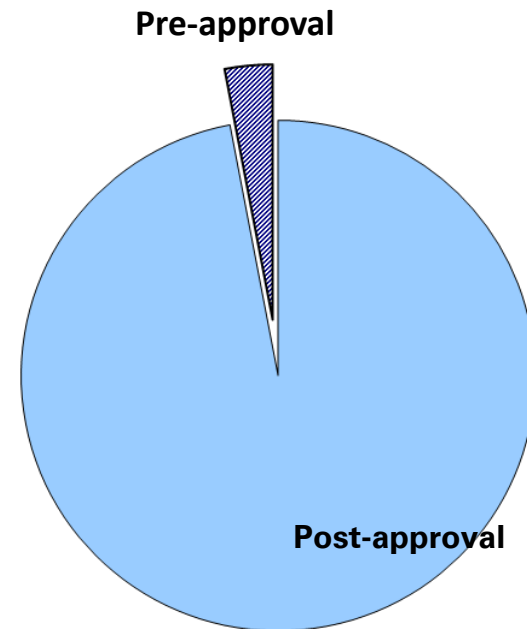
Product Lifecycle

PPPQMS Drives Change Management

- Use QRM to establish the control strategy
  - ✓ What and when to monitor / measure / test
  - ✓ Based on critical product quality attributes and the critical process parameters to deliver them

- *"Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation."* [ICH Q10]
  - ✓ Reduce and control variation to appropriate levels
  - ✓ Drives continual improvement
  - ✓ Implement changes as needed though Change Management system

- Confirm and maintain a state of control
  - ✓ Feed-back Loop: *"The modification or control of a process or system by its results or effects."* [ICH Q10]
  - ✓ Feed-forward Loop: *"The modification or control of a process using its anticipated results or effects."* [ICH Q10]

- Provide knowledge to enhance process understanding

PPPQMS Inputs....May Trigger Risk Review, CAPA, and/or Change Management

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- Nonconformances, discrepancies, deviations, failures, recalls
- Product Quality Data
- Process monitoring results
  - e.g., batch data, trend analysis
- Equipment or Facility issues (e.g., deviations, malfunctions, maintenance)
- Raw Material Issues
- Regulatory Findings (local or at another site)
- Audits and self-inspections
- Complaints/Returns
- Stability Testing results

Trend/Assess Data, Monitor

Evaluate periodically (at least annually per 21 CFR 211.180(e)) to determine the need for changes in drug product specifications or manufacturing and control procedures

Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to *determine the need for changes in drug product specifications or manufacturing or control procedures.*

Building knowledge…
Effective monitoring & control systems

- *"To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes."*

- *"A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas"*

[ICH Q10]

PPPQMS ensures Knowledge Management and Communication of Risk

- An effective monitoring system ensures a state of control is maintained

- The monitoring system should use QRM
  - ✓ Identify sources of variation
  - ✓ Include feedback from internal and external sources
  - ✓ *"Answer the "What might go wrong?" question, including identifying the possible consequences"* [Q9 Risk identification]

- Provide knowledge to enhance process understanding
  - ✓ Mange the knowledge gained and communicate the risk or changing risk

Building Knowledge…Trend/Assess Data, Monitor

- *"Select, evaluate and interpret trend results of data within the product quality review"* [ICH Q9]
  - ✓ Analyze data gathered from monitoring processes

- *"To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)".* [ICH Q9]
  - ✓Timely monitoring of critical operating and performance parameters
  - ✓Investigate problems for root cause and implement corrective action
  - ✓Are changes needed?

Effective CAPA drives Change Management

"The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding."

[ICH Q10, 3.2.2 Corrective and Preventive Action (CAPA) System]

Effective CAPA drives Change Management

- Effective Investigation of non-conformances
  - ✓ Structured investigations to seek root cause
  - ✓ Use QRM to ensure degree and formality is commensurate with level of risk
  - ✓ Should result in enhanced knowledge and improvement
  - ✓ Focus on preventative actions
  - ✓ Do they investigate to improve knowledge or simply build arguments for release of product

- Reactive usage of knowledge
  - ✓ Deviations, rejections, complaints, recalls, observations from audits and inspections

- Proactive usage of knowledge
  - ✓ feedback from trends

Getting to Root Causes Drives Continual Improvement

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- A large number of manufacturing **failures** can be traced to failures in the firm's **quality system.**

- In some cases, the quality system **ignored** or **failed** to follow-up on customer complaints.

- In other cases, multiple repeated deviations were **treated as separate** incidents, rather than an **obvious trend.**

- Another reoccurring theme has been **investigations "to nowhere"** ... end with no additional understanding or insight into why the problem may have occurred and thus no hope for prevention.

- Without the root cause of the problem identified there is a failure in assuring continual improvement of the process

In Some Cases, Very Substantial Changes Are Needed

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"OOS results may indicate a flaw in product or process design. For example, a lack of robustness in product formulation, inadequate raw material characterization or control, substantial variation introduced by one or more unit operations of the manufacturing process, or a combination of these factors can be the cause of inconsistent product quality. In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality."

[FDA OOS Guidance, 2006]

Quality Risk Management (QRM)

"Quality Risk Management is a process consisting of well defined steps which when taken in sequence, support *better decision making* *by contributing to a* *greater insight into risks and their impacts**. It includes elements such as risk identification, assessment, mitigation, elimination and communication."*

[Final Concept Paper Q9: Quality Risk Management]

Good Lifecycle Decision Making via Quality Risk Management (QRM)

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- The output/results of the risk management process should be reviewed to take into account *new knowledge* and *experience*.

- Once a quality risk management process has been initiated, that process should continue to be utilized for **events that might impact the original quality risk management decision.**
  - ✓ **planned** (e.g., results of product review, inspections, audits, change control)
  - ✓ **unplanned** (e.g., **root cause from failure investigations**, recall).

- The frequency of any review should be based upon the level of risk.

- **Risk review** might include **reconsideration of risk acceptance decisions** (Section 4.4 Risk Control).
 - ✓ The purpose of risk control is to reduce the risk to an acceptable level

[ICH Q9]

QRM Enables Change Management

- To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing
  - ✓ Use of prior knowledge – development, other manufacturing locations, similarities with other products
- To evaluate the impact of the changes on the availability of the final product;
- To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers;
- To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

[ICH Q9]

QRM Enables Change Management
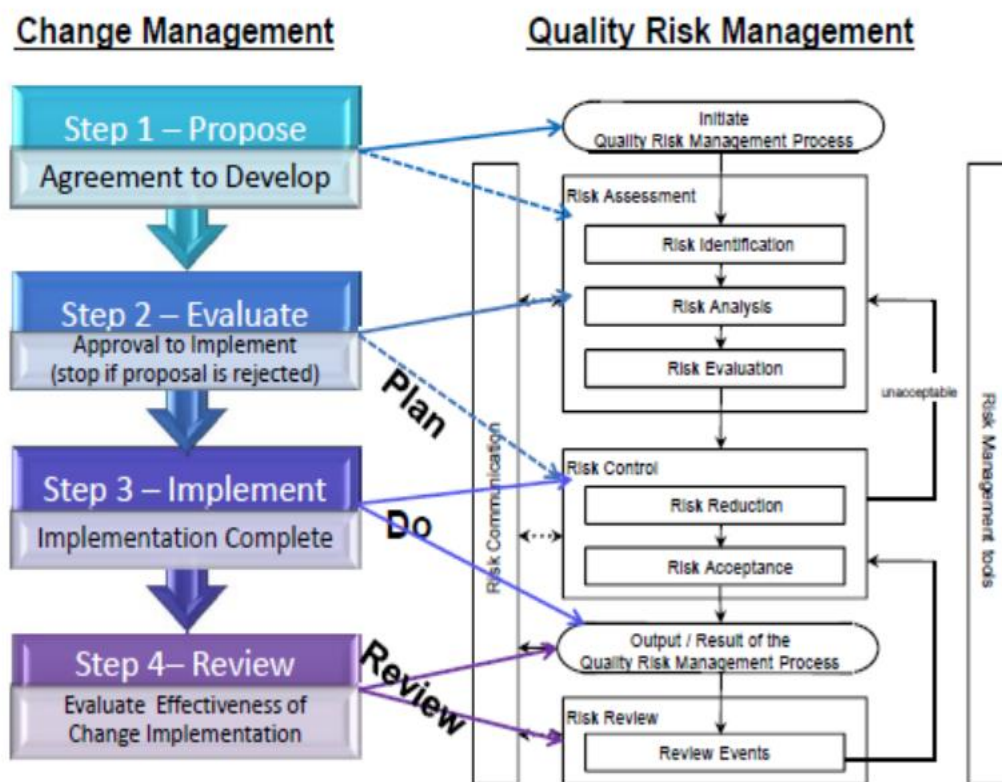
Applying Quality Risk Management (QRM) to Change Management

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Elements of Change Management Program:

1. Estimate risk posed by a proposed change

   ✓ *Impact gauged by probability, severity, detectability*

   ✓ *What is the potential impact?*

   ✓ *What might go wrong?*

2. Determine needed scrutiny

   ✓ What data needs to be developed?

   ✓ How will it be measured?

3. Document the change, the results, and QA approval

   ✓ Output should include understanding of adequacy of controls and additional ones as necessary

4. Evaluate effectiveness

Is Change Management Causing or Preventing Drug Shortages?

FDA's Frequently Asked Questions about Drug Shortages

Q. What is the major reason for these shortages?

A: A major reason for these shortages has been quality/manufacturing issues. However there have been other reasons such as production delays at the manufacturer and delays companies have experienced receiving raw materials and components from suppliers. Discontinuations are another factor contributing to shortages. FDA can't require a firm to keep making a drug it wants to discontinue. Sometimes these older drugs are discontinued by companies in favor of newer, more profitable drugs.

https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q3

Take home message

"Your life doesn't get better by chance, it gets better by change."-Jim Rohm

Thank you for your attention

ANY QUESTIONS?