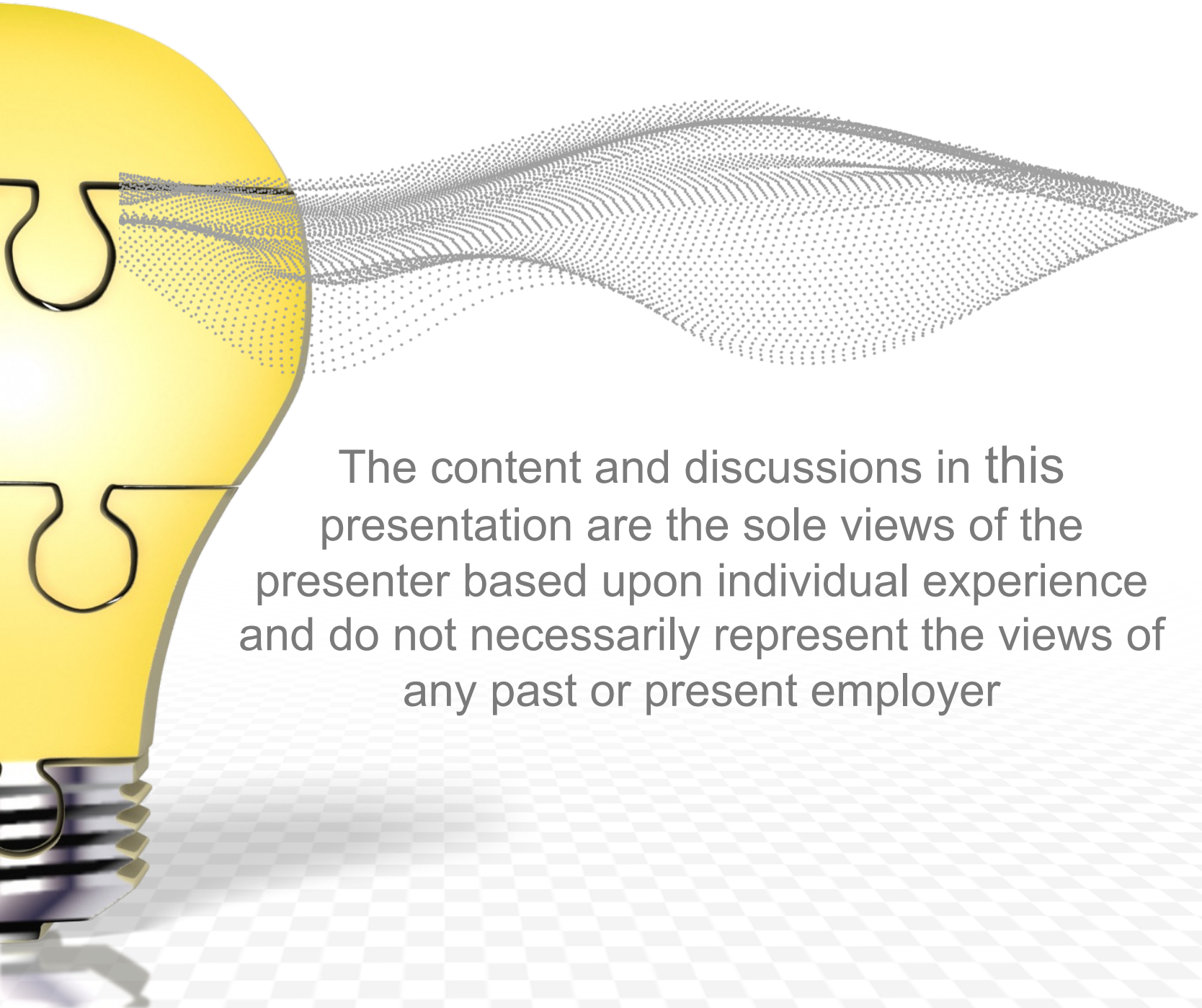
Conduct a Change Control Impact Assessment

Dawn Marshall (Tavalsky)



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Agenda

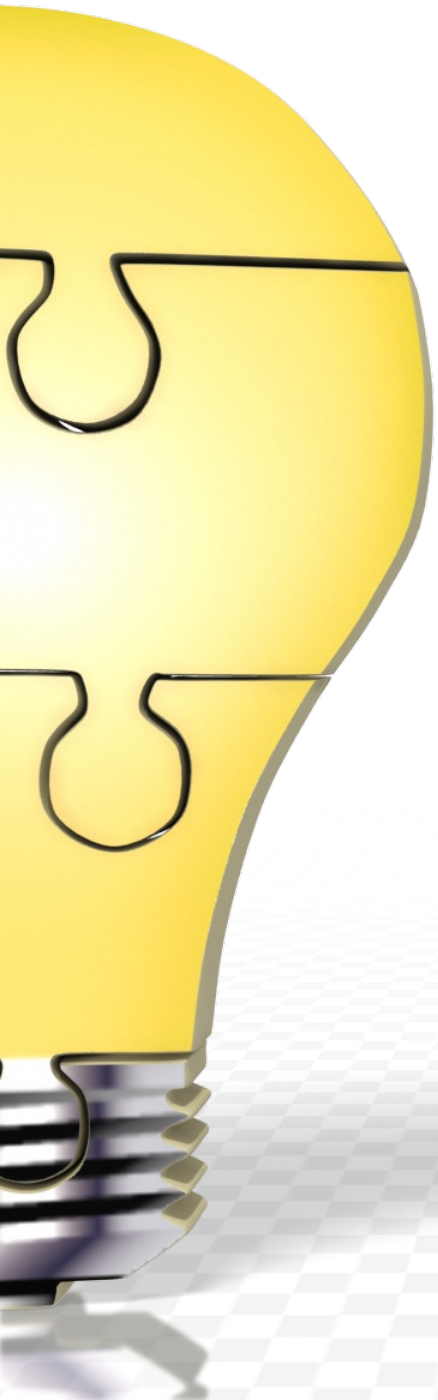
Part 1 – **The Change Control System**

- Why is a change control system needed?
- When does the change control system need to be implemented?
- Project change control versus quality change control
- Review an example of generic change control process flow
- Paper versus electronic change control systems

Part 2 – **Change Control Impact Assessments**

- Providing detail in the change control
- Determining departments required to perform assessments
- The focus of the assessment
- Developing an assessment checklist for each department perspective
- Learning from mistakes of poor assessments

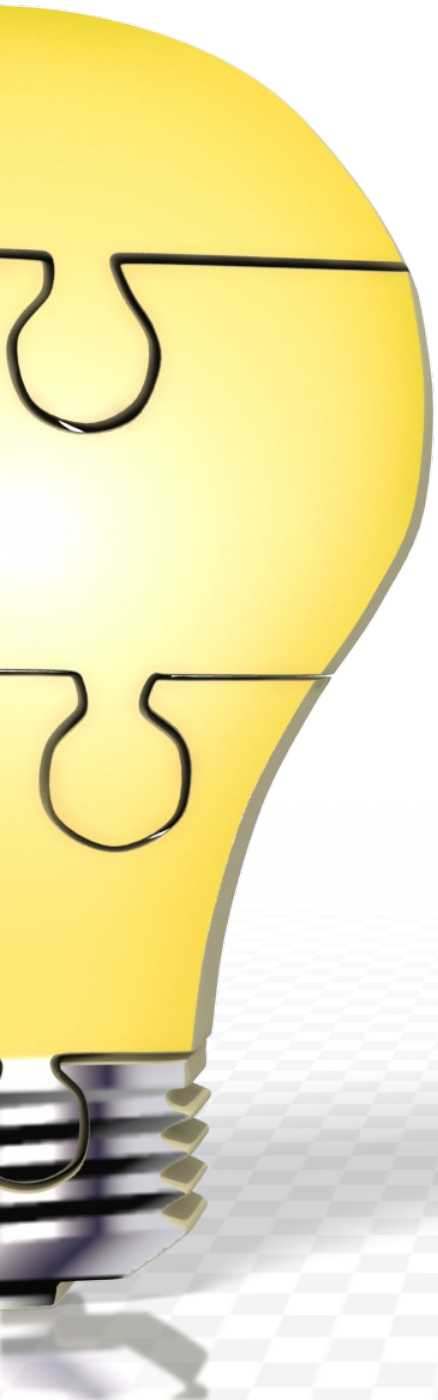
Part 1



What is Change Control?

The methods and procedures you establish to identify, assess, approve, and implement changes to:

- A Product, and the product's:
  - Packaging
  - Labeling
  - Manufacture
  - Testing

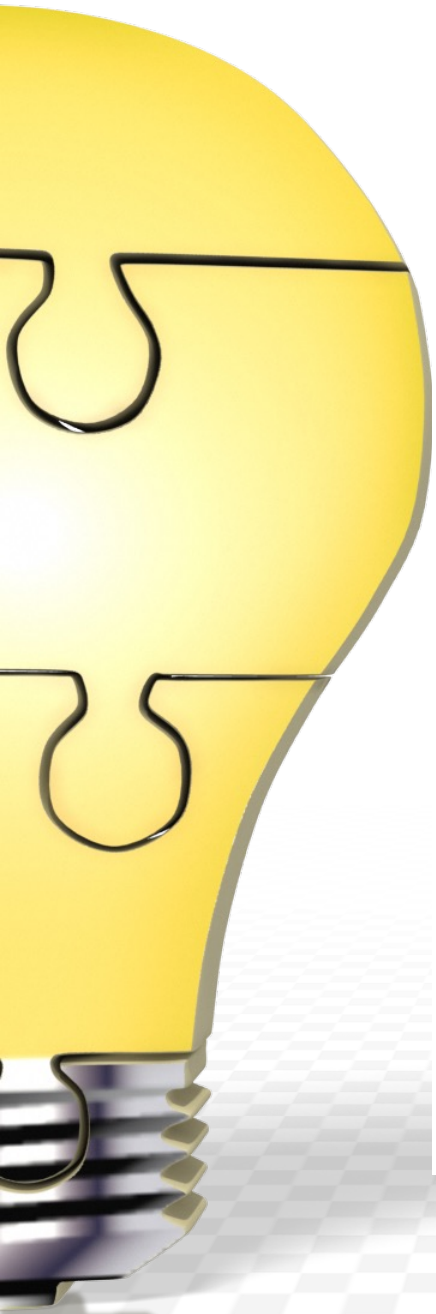


There are two general rules of change control every company needs to adopt.

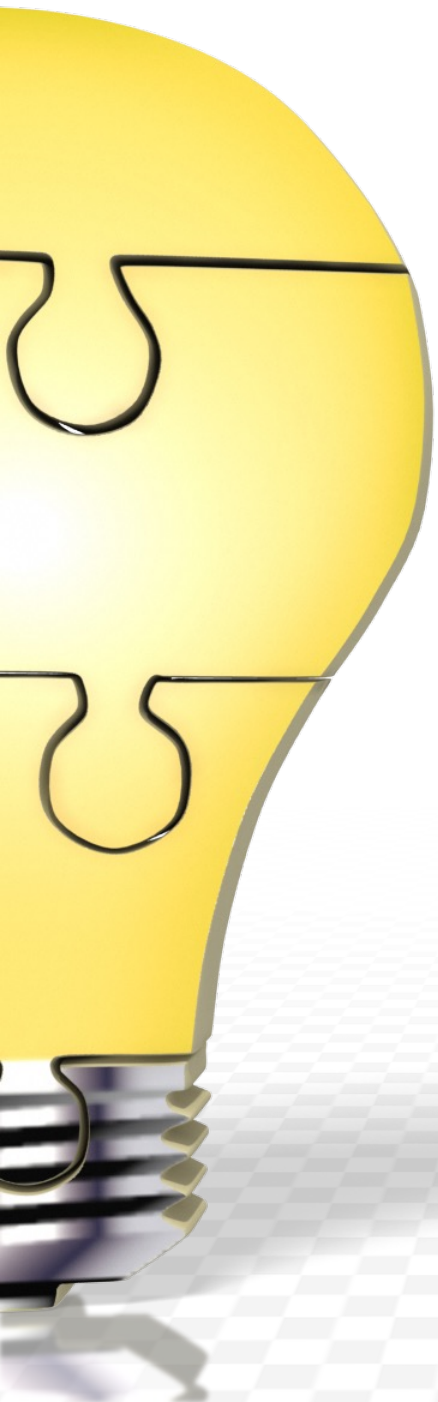
First Rule: The only constant is change

Second Rule: Deal with it.

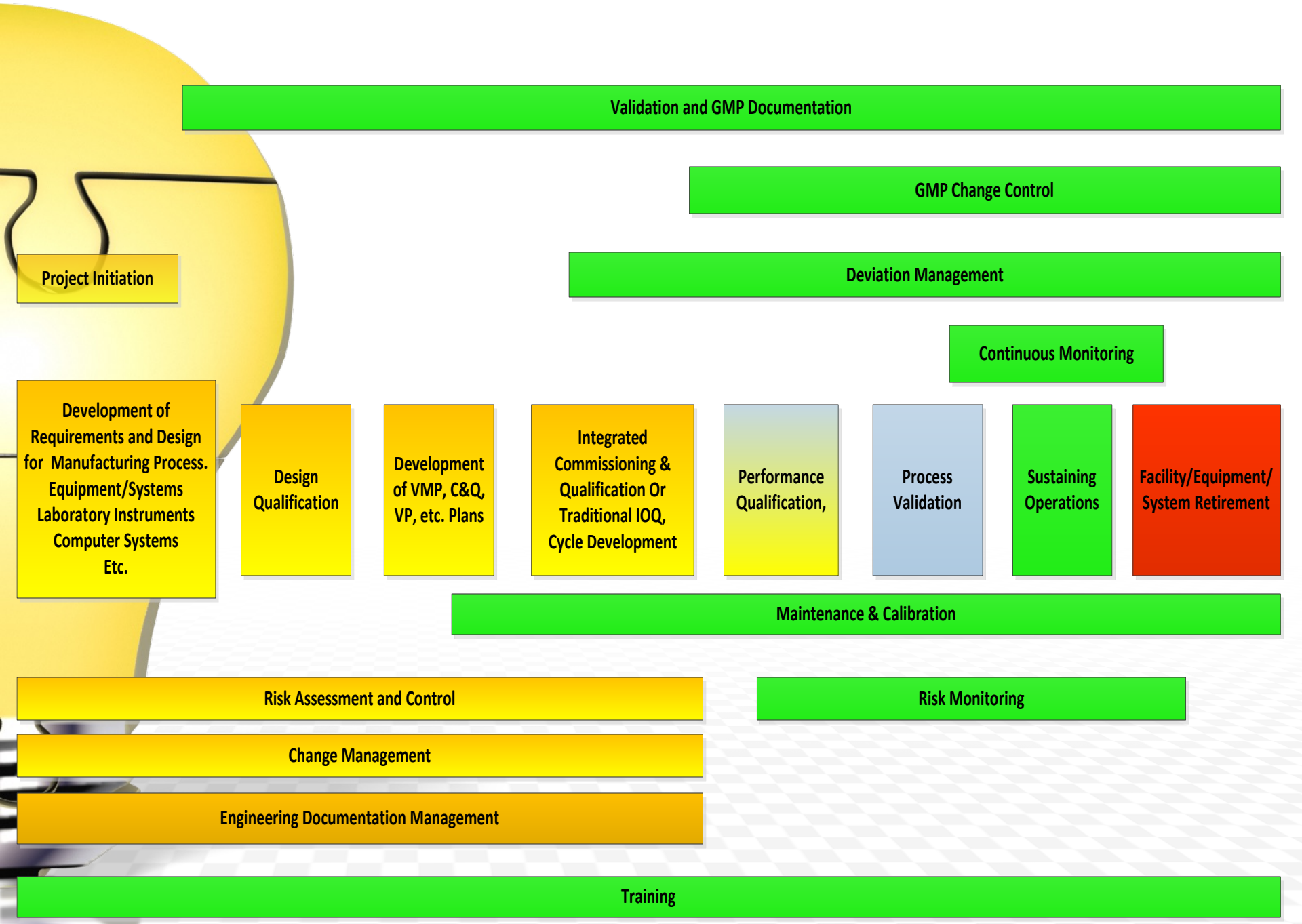
How you deal with change and the processes you have in place to address changes will determine your overall pain level

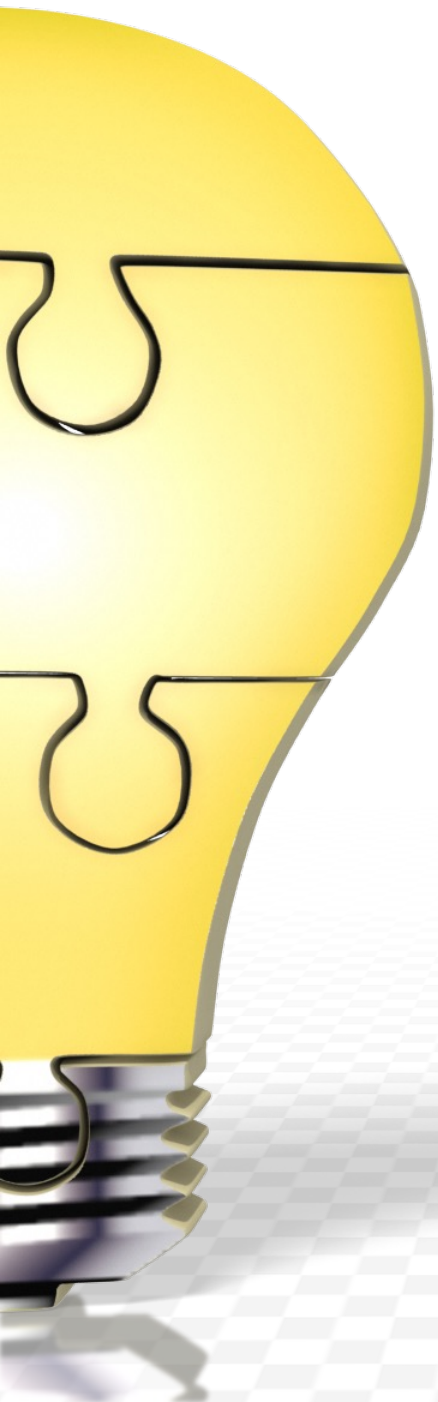


"I want you to find a bold and innovative way to do everything exactly the same way it's been done for 25 years."



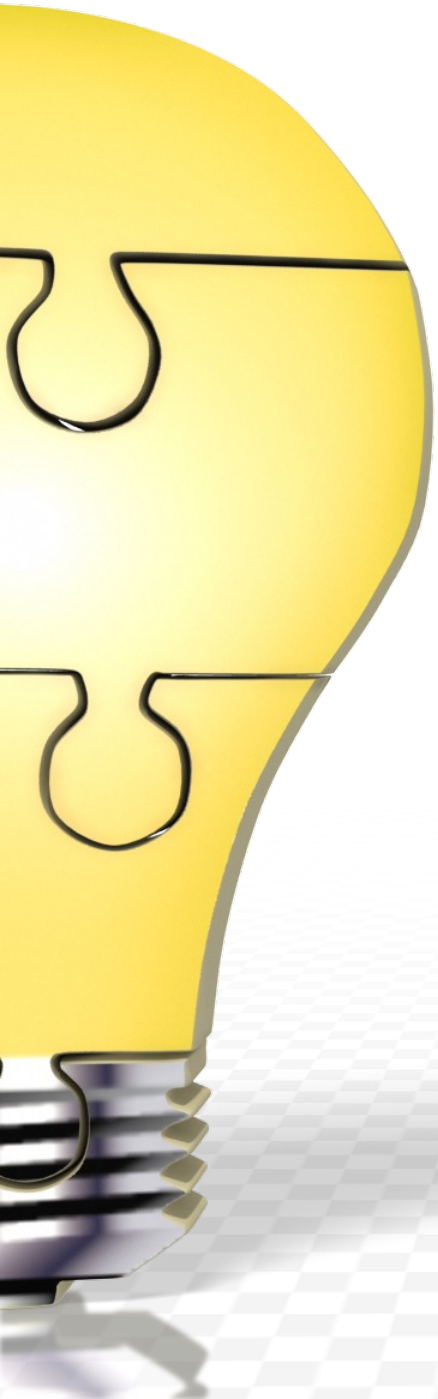
When Does Change Control Need to be Implemented?


Validation and GMP Documentation
GMP Change Control
Project Initiation
Deviation Management
Continuous Monitoring
Development of Requirements and Design for Manufacturing Process. Equipment/Systems Laboratory Instruments Computer Systems Etc.
Design Qualification
Development of VMP, C&Q, VP, etc. Plans
Integrated Commissioning & Qualification Or Traditional IOQ, Cycle Development
Performance Qualification,
Process Validation
Sustaining Operations
Facility/Equipment/ System Retirement
Maintenance & Calibration
Risk Assessment and Control
Risk Monitoring
Change Management
Engineering Documentation Management
Training



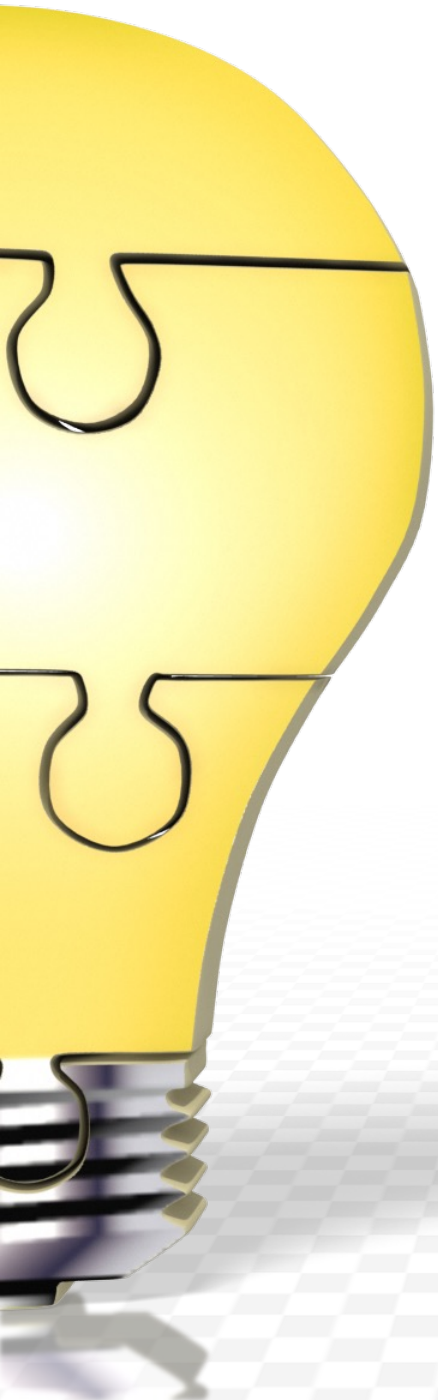
Difference Between:

1. Quality Change Control
2. Project Change Control



Failure to establish a system, appropriately that will address, assess and control changes can:

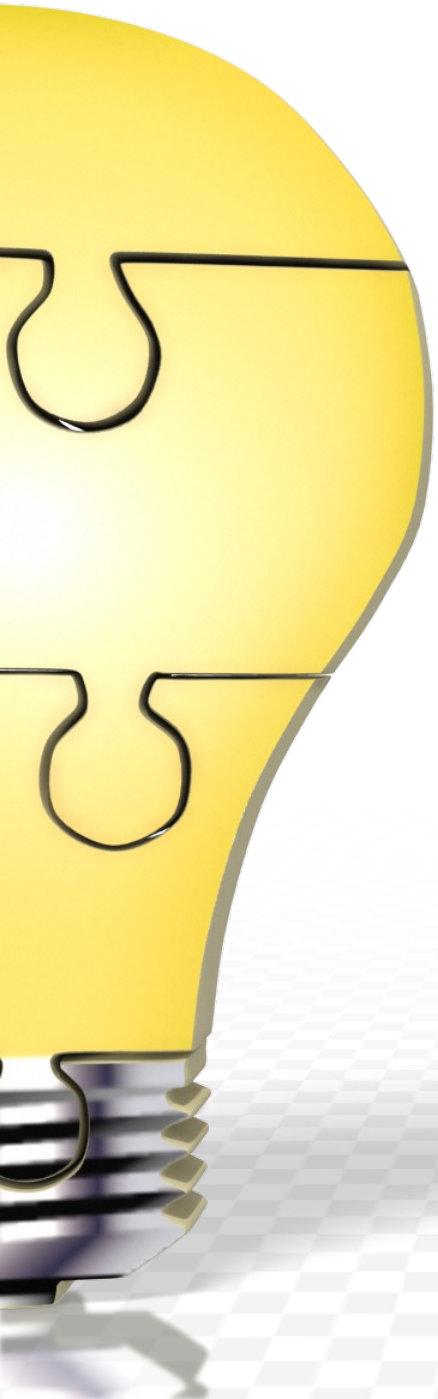
- Lead to the development of product which is not “suitable for use”
- Result in an inability to correct issues once a product is on market
- Result in audit observations for violations of CFR’s and ISO standards



If you don’t have control over changes in product design it makes it much harder to fix any issues which may arise after product launch.

You need to be able to trace:

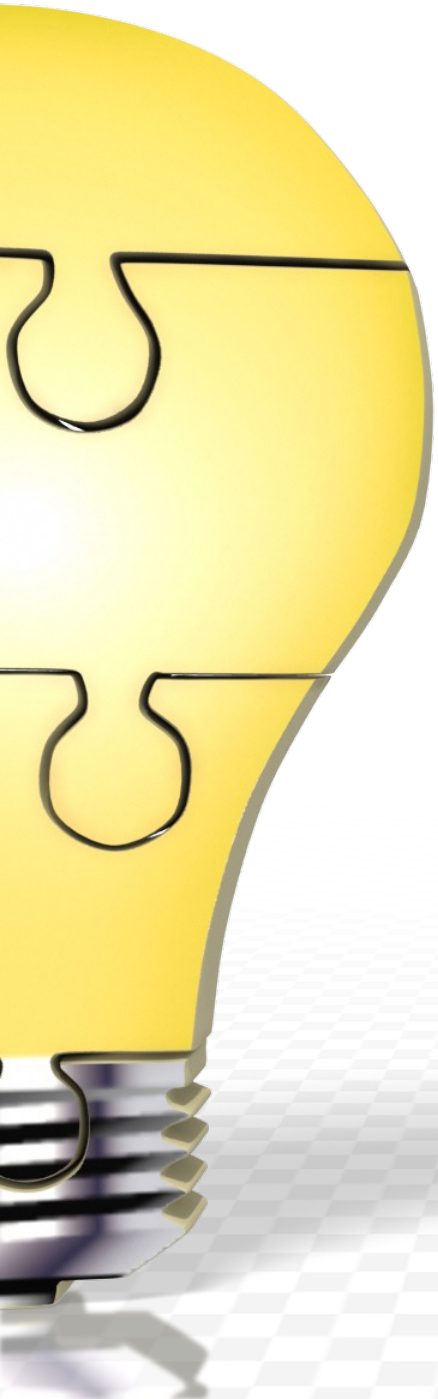
- Design decisions
- Formulation changes
- Vendor changes
- Manufacturing changes



Regulatory Requirements

21 CFR PART 820 Quality System Regulation,
Sec. 820.30 Design Controls

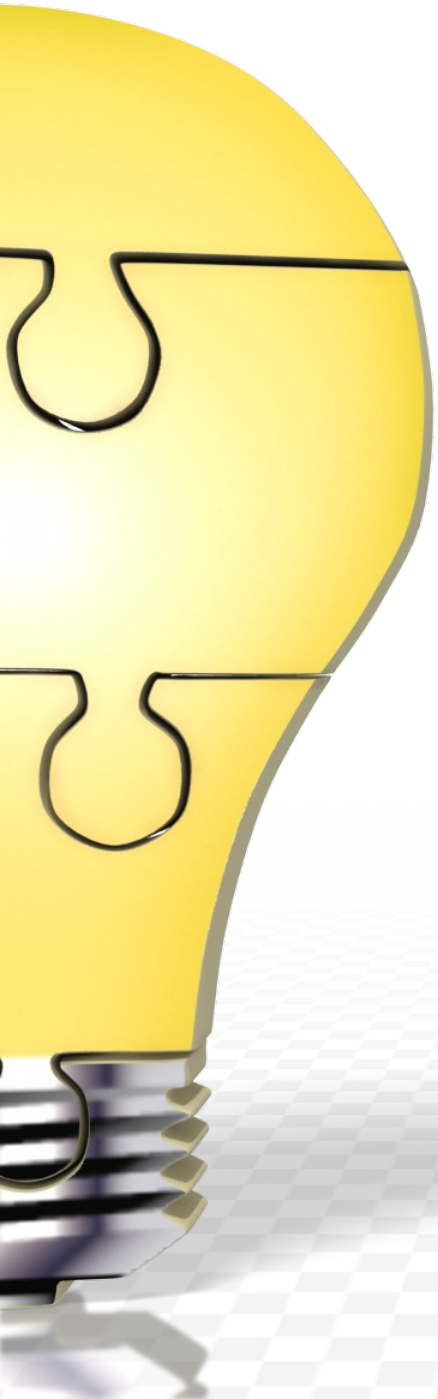
- (i)*Design changes.* Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.



Regulatory Requirements

21 CFR PART 820 Quality System Regulation,
Sec. 820.40 Document controls

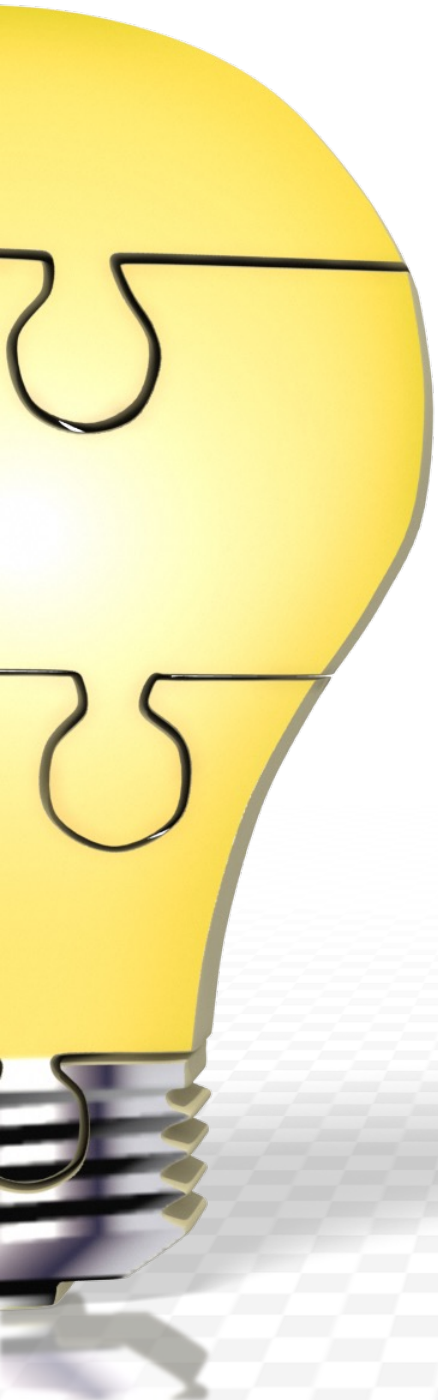
- (b)*Document changes.* Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.



From ISO 13485:2003(E)

4.2.3 Control of documents

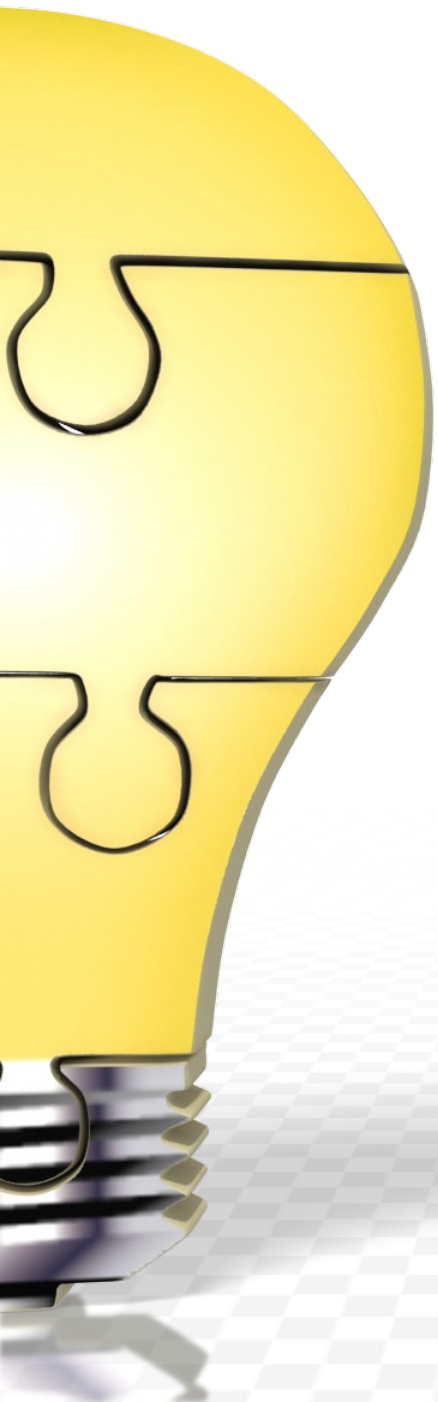
- The organization shall ensure that changes to documents are reviewed and approved either by the original approving function or another designated function which has access to pertinent background information upon which to base its decisions.



From 21 CFR PART 211: CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

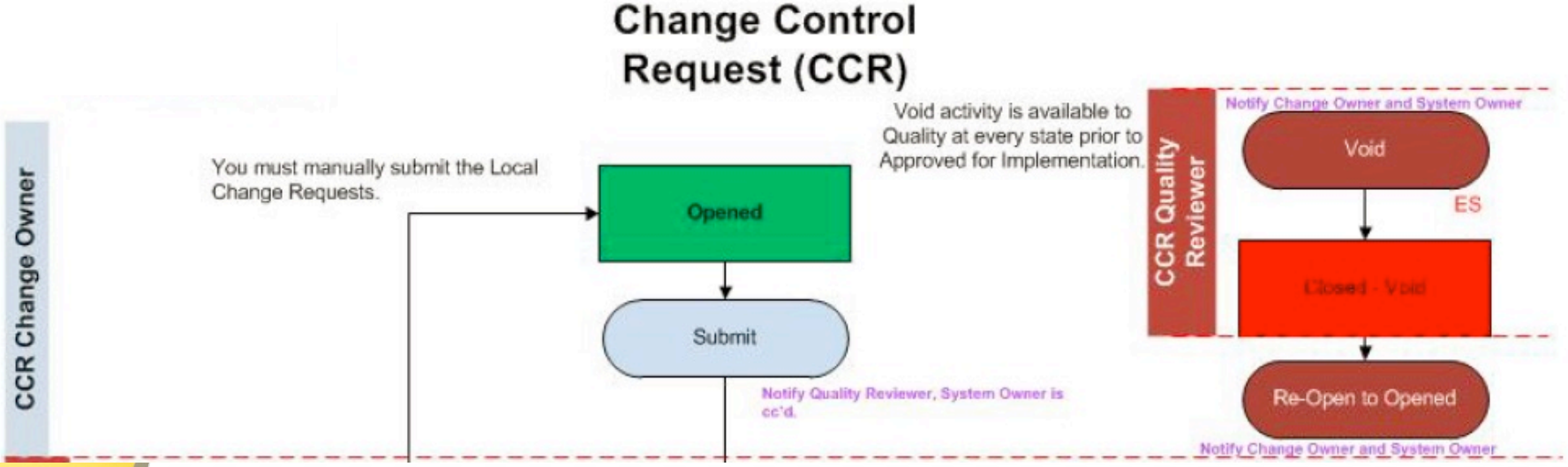
Subpart F-Production and Process Controls

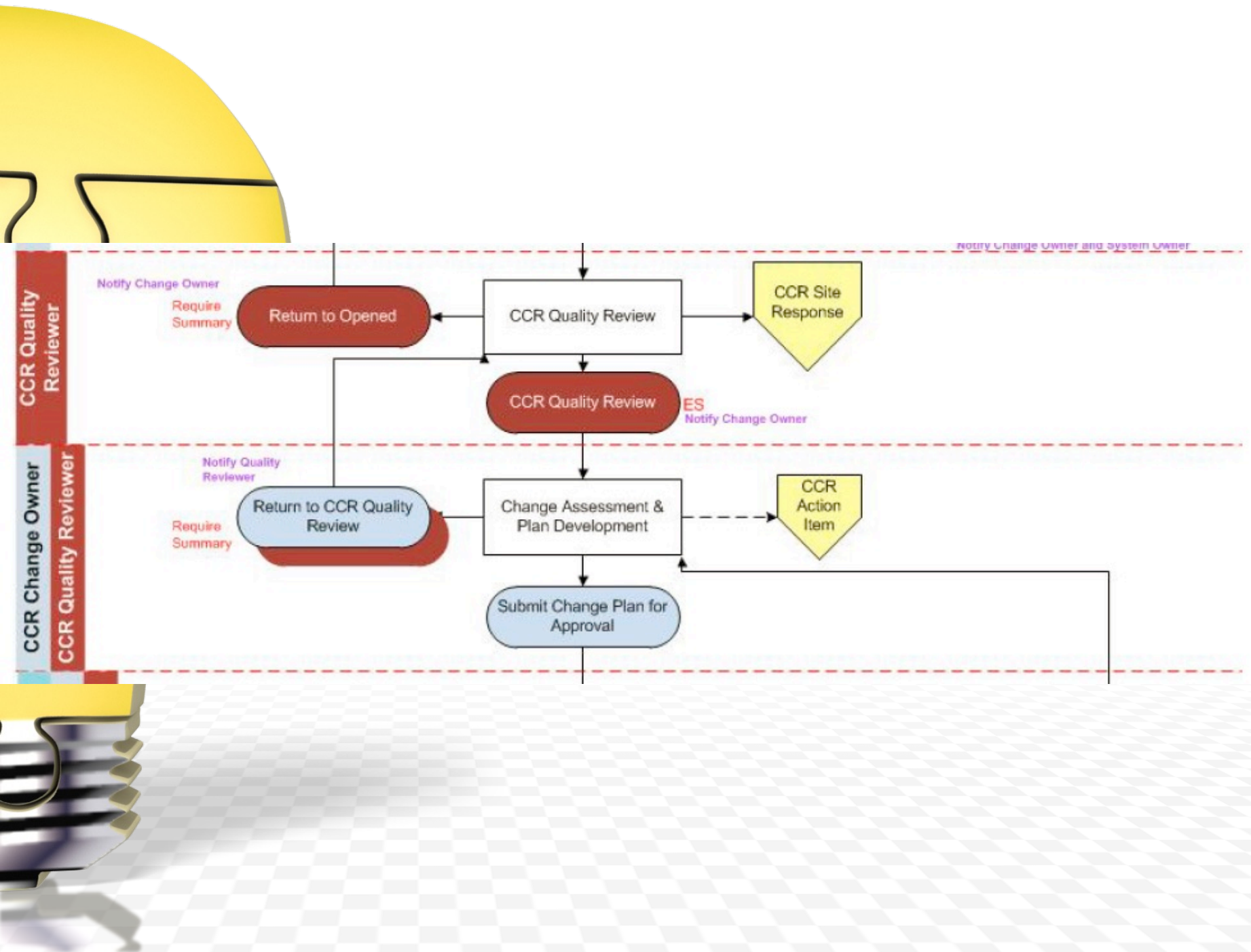
- **(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.**

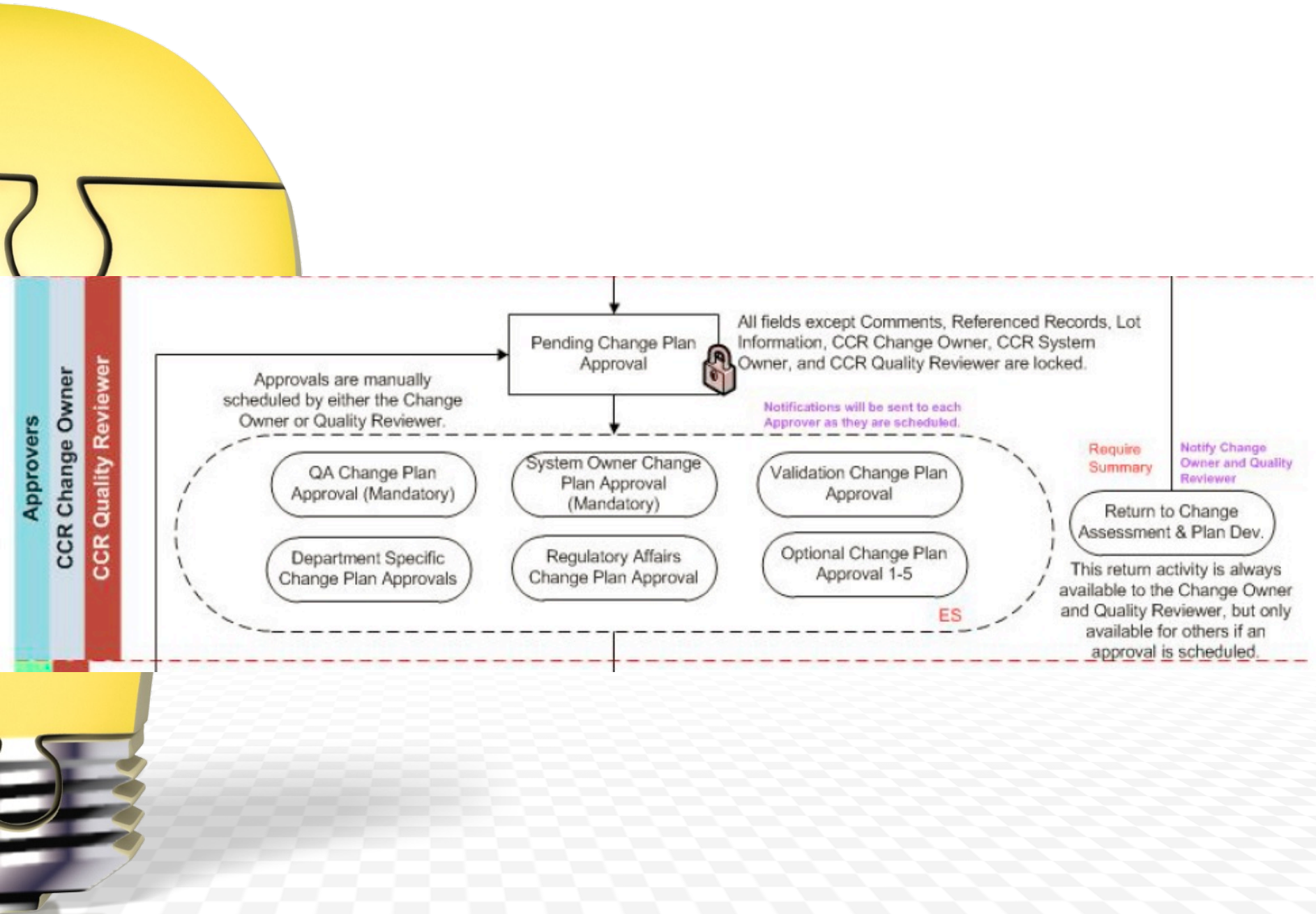


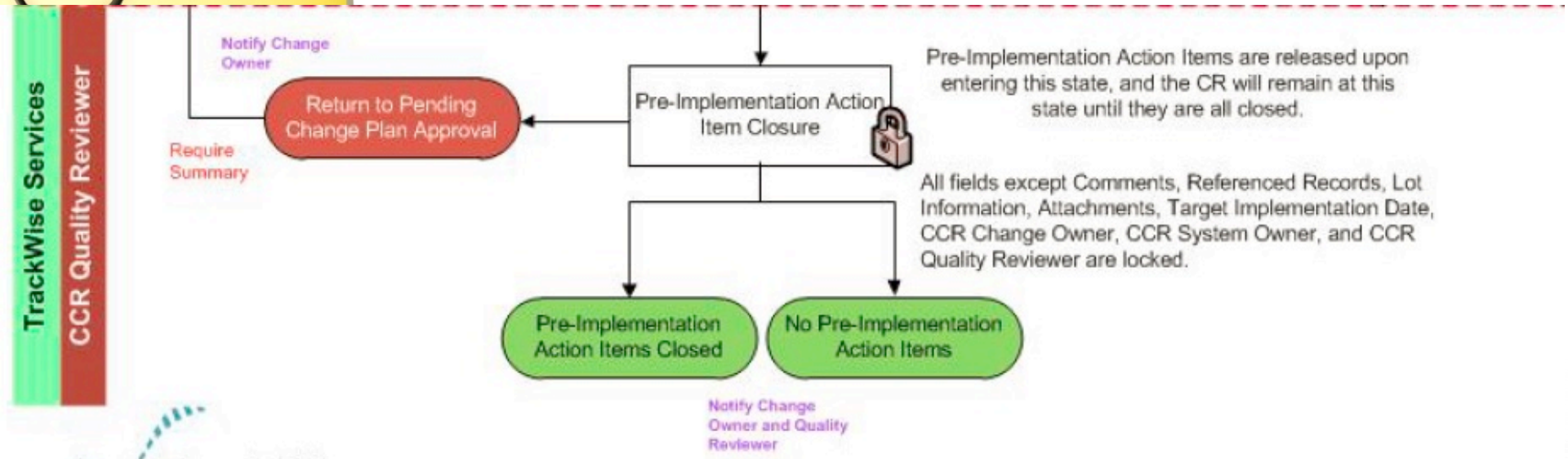
Example Change Control Process Flow

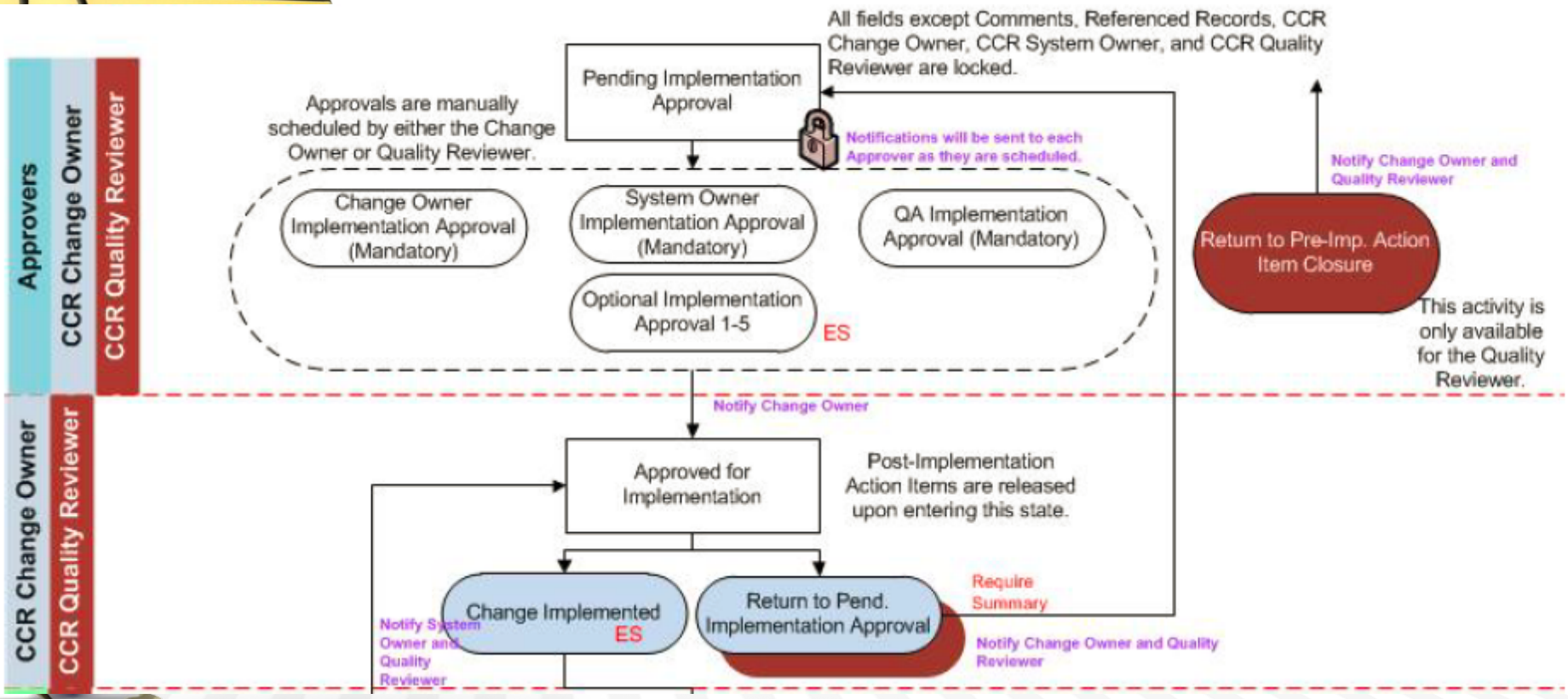
Change Control Request (CCR)

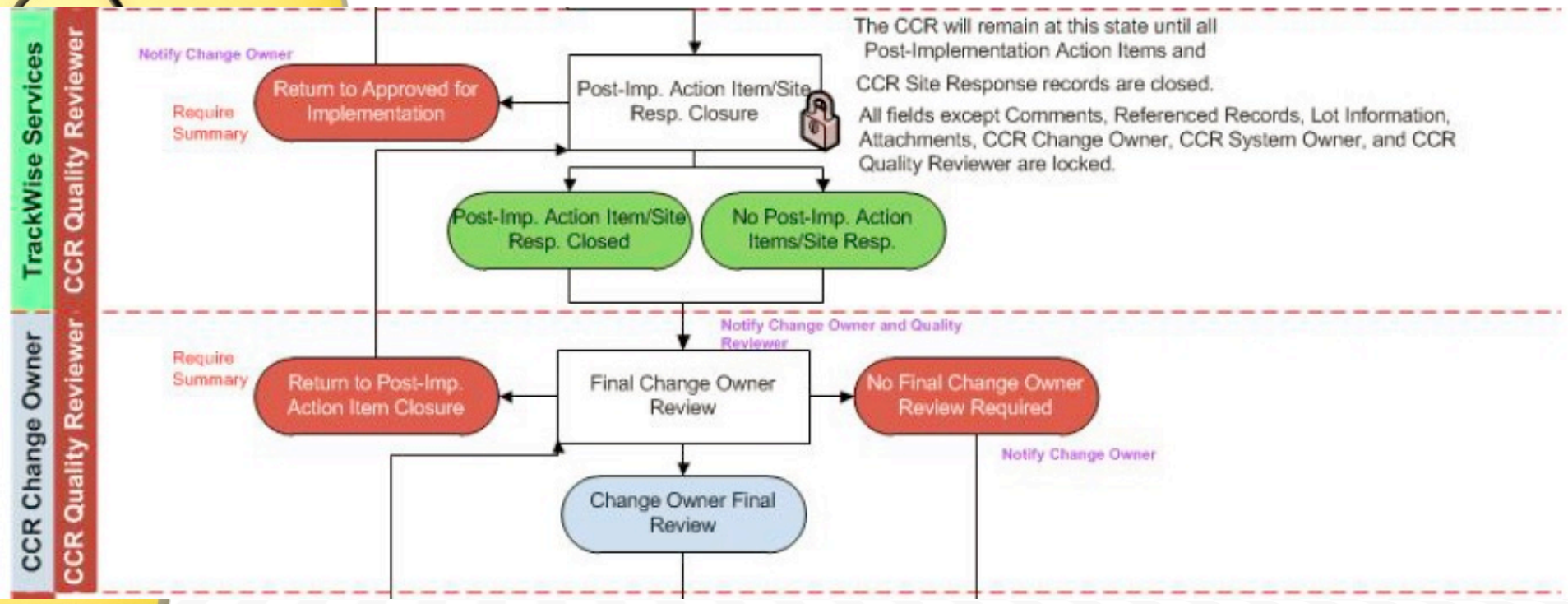


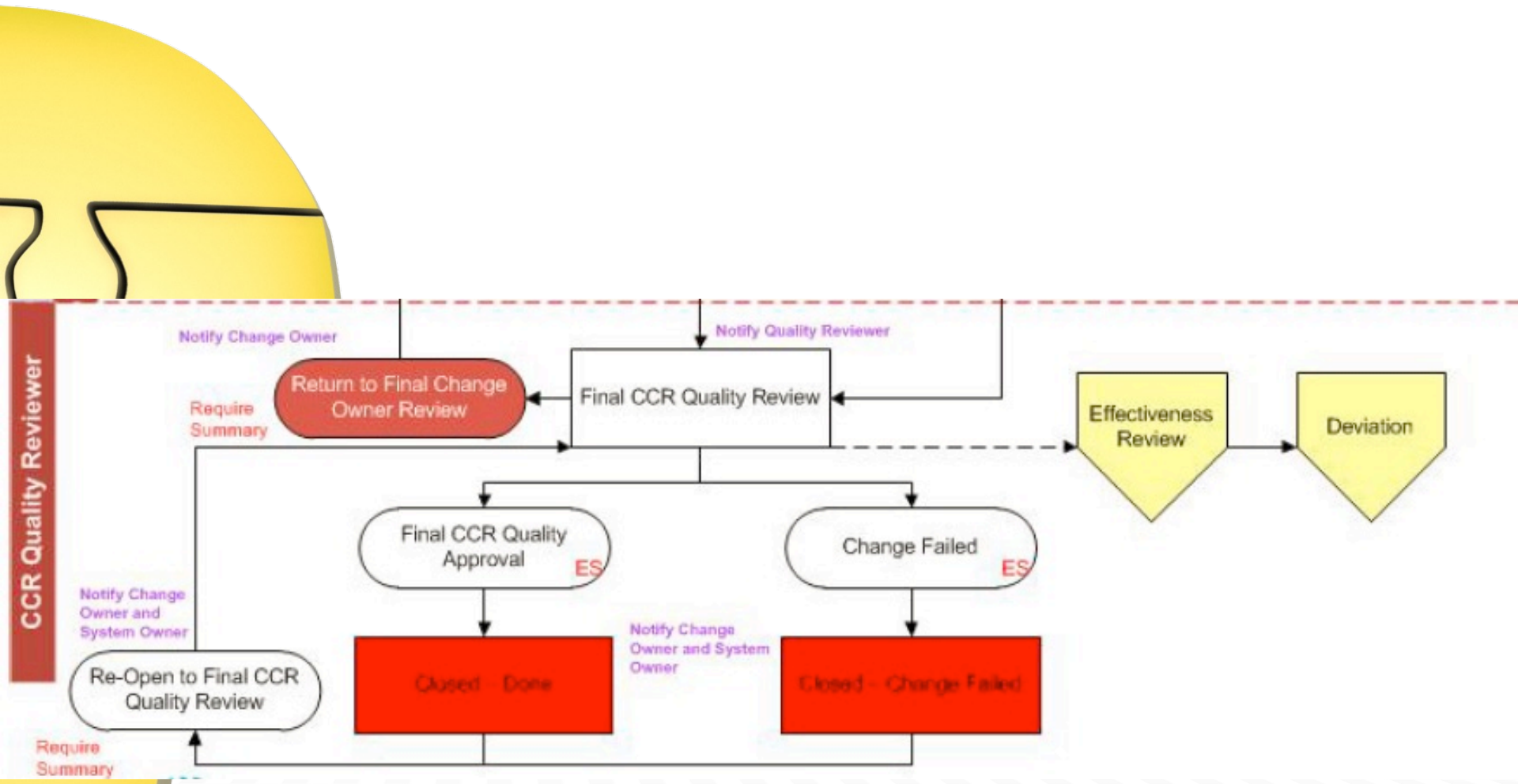

CCR Quality Reviewer
CCR Change Owner
CCR Quality Reviewer
Notify Change Owner
Require Summary
Return to Opened
CCR Quality Review
CCR Site Response
CCR Quality Review
ES
Notify Change Owner
Notify Quality Reviewer
Require Summary
Return to CCR Quality Review
Change Assessment & Plan Development
CCR Action Item
Submit Change Plan for Approval

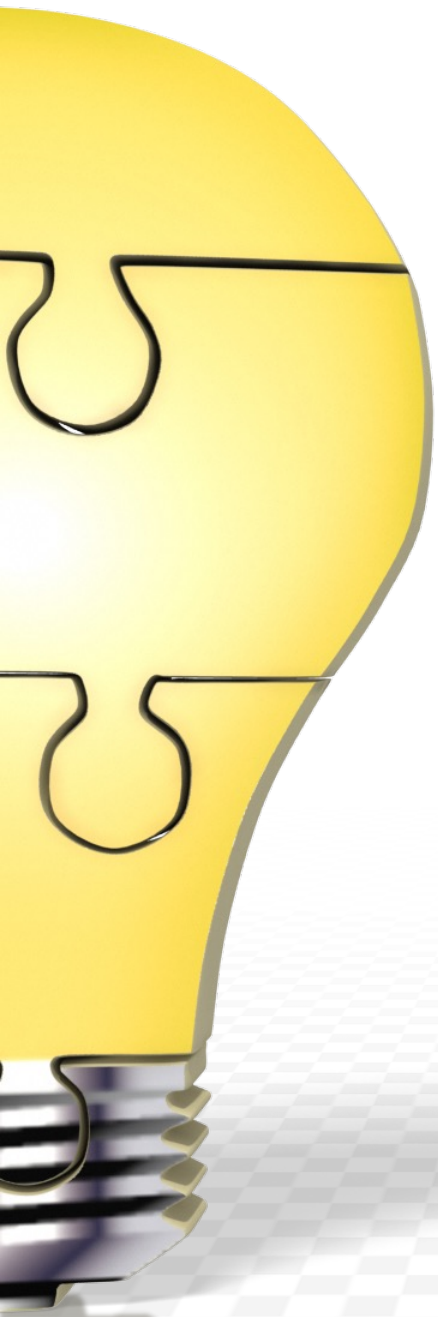

Approvers
CCR Change Owner
CCR Quality Reviewer
Pending Change Plan Approval
All fields except Comments, Referenced Records, Lot Information, CCR Change Owner, CCR System Owner, and CCR Quality Reviewer are locked.
Approvals are manually scheduled by either the Change Owner or Quality Reviewer.
Notifications will be sent to each Approver as they are scheduled.
QA Change Plan Approval (Mandatory)
System Owner Change Plan Approval (Mandatory)
Validation Change Plan Approval
Department Specific Change Plan Approvals
Regulatory Affairs Change Plan Approval
Optional Change Plan Approval 1-5
ES
Require Summary
Notify Change Owner and Quality Reviewer
Return to Change Assessment & Plan Dev.
This return activity is always available to the Change Owner and Quality Reviewer, but only available for others if an approval is scheduled.


TrackWise Services
CCR Quality Reviewer
Notify Change Owner
Return to Pending Change Plan Approval
Require Summary
Pre-Implementation Action Item Closure
Pre-Implementation Action Items are released upon entering this state, and the CR will remain at this state until they are all closed.
All fields except Comments, Referenced Records, Lot Information, Attachments, Target Implementation Date, CCR Change Owner, CCR System Owner, and CCR Quality Reviewer are locked.
Pre-Implementation Action Items Closed
No Pre-Implementation Action Items
Notify Change Owner and Quality Reviewer

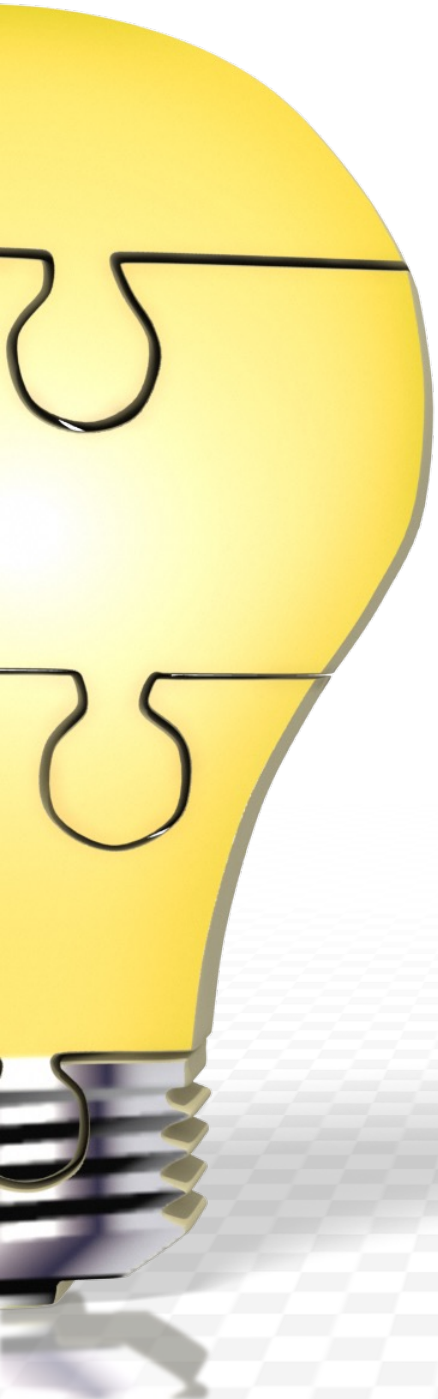

Approvers
CCR Change Owner
CCR Quality Reviewer
All fields except Comments, Referenced Records, CCR Change Owner, CCR System Owner, and CCR Quality Reviewer are locked.
Pending Implementation Approval
Approvals are manually scheduled by either the Change Owner or Quality Reviewer.
Notifications will be sent to each Approver as they are scheduled.
Change Owner Implementation Approval (Mandatory)
System Owner Implementation Approval (Mandatory)
QA Implementation Approval (Mandatory)
Optional Implementation Approval 1-5
ES
Notify Change Owner and Quality Reviewer
Return to Pre-Imp. Action Item Closure
This activity is only available for the Quality Reviewer.
Notify Change Owner
CCR Change Owner
CCR Quality Reviewer
Approved for Implementation
Post-Implementation Action Items are released upon entering this state.
Change Implemented
ES
Return to Pend. Implementation Approval
Require Summary
Notify System Owner and Quality Reviewer
Notify Change Owner and Quality Reviewer


TrackWise Services
CCR Quality Reviewer
CCR Change Owner
CCR Quality Reviewer
Notify Change Owner
Require Summary
Return to Approved for Implementation
Post-Imp. Action Item/Site Resp. Closure
The CCR will remain at this state until all Post-Implementation Action Items and CCR Site Response records are closed.
All fields except Comments, Referenced Records, Lot Information, Attachments, CCR Change Owner, CCR System Owner, and CCR Quality Reviewer are locked.
Post-Imp. Action Item/Site Resp. Closed
No Post-Imp. Action Items/Site Resp.
Notify Change Owner and Quality Reviewer
Require Summary
Return to Post-Imp. Action Item Closure
Final Change Owner Review
No Final Change Owner Review Required
Notify Change Owner
Change Owner Final Review


CCR Quality Reviewer
Notify Change Owner
Notify Quality Reviewer
Return to Final Change Owner Review
Final CCR Quality Review
Require Summary
Effectiveness Review
Deviation
Final CCR Quality Approval
ES
Change Failed
ES
Notify Change Owner and System Owner
Re-Open to Final CCR Quality Review
Closed - Done
Notify Change Owner and System Owner
Closed - Change Failed
Require Summary



Paper Versus Electronic Change Control Systems



How To Manage Change

What is the change?

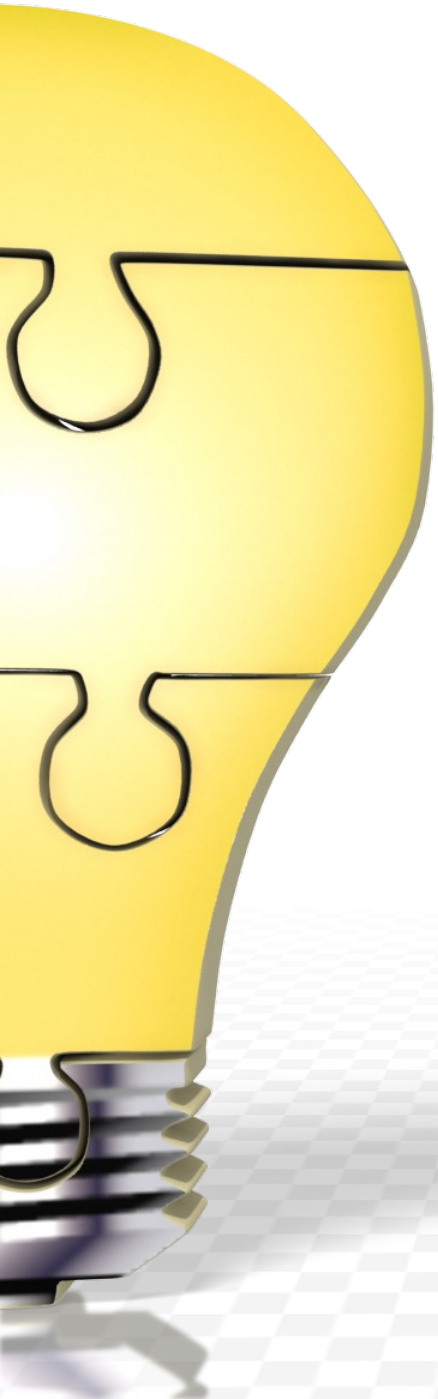
- This is a brief but complete description of what is changing.

Why is the change needed?

- There has to be a sound, justified reason for making the change. With EVERY change – there is RISK – we shouldn't take any risk without good justification and sound risk remediation.

Why is the change Ok to make?

- If I make this change, will it fix the issue and not break anything else or create non-compliance issues or gaps.



How To Manage Change

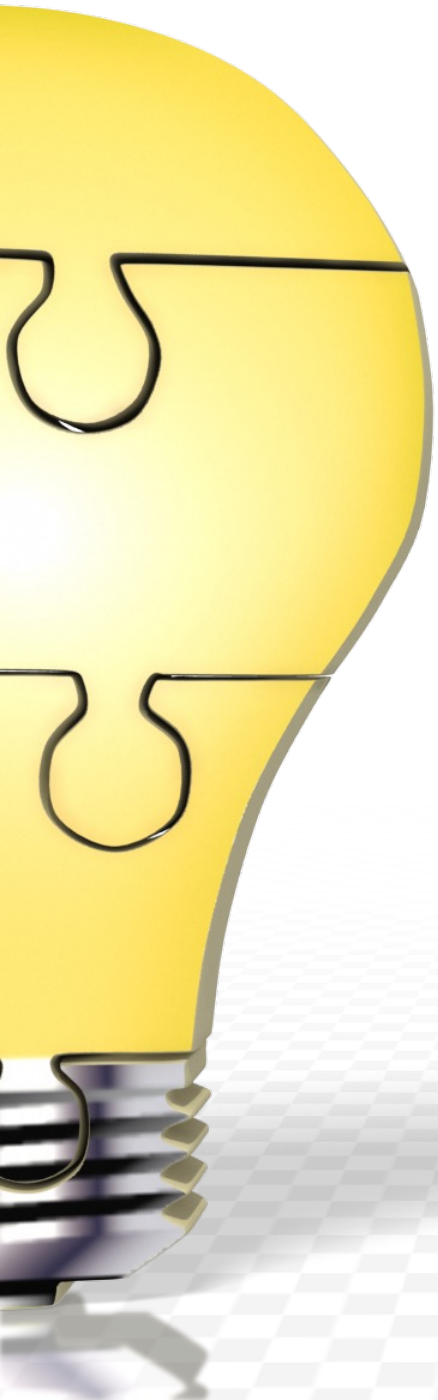
Rule number 1:

- Don’t try to make the impact decision by yourself.

Rule number 2:

See rule number 1.

Put a team together to evaluate changes and have a **process**.

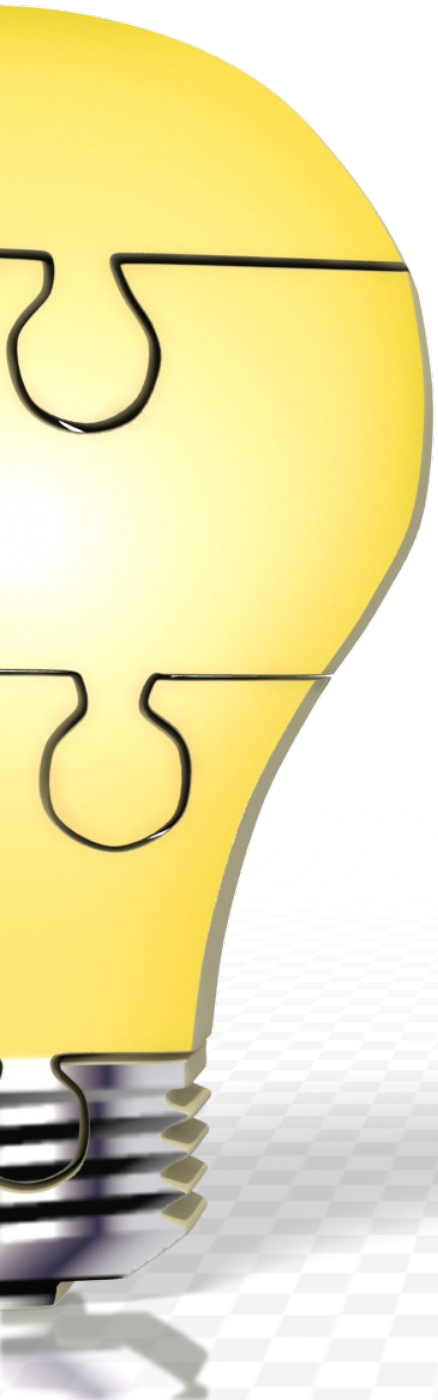


The Change Team – Who

Who you put on the team will depend on where in development (or on market) you are and how complex the change is.

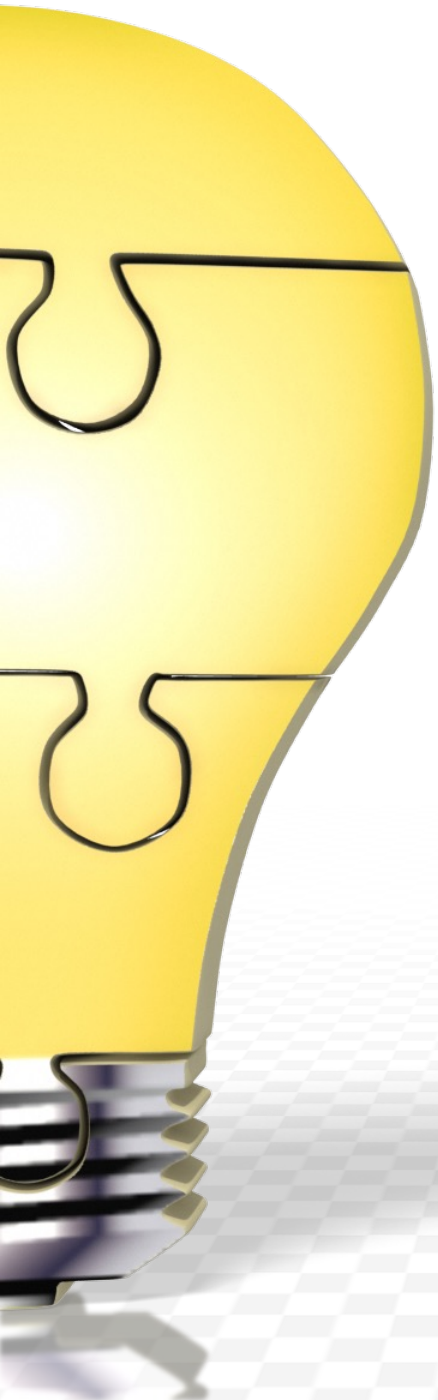
Some departmental areas to consider:

- Technical
- Validation
- Quality Assurance
- Quality Control
- Regulatory Affairs
- R&D
- Operations
- Clinical Affairs
- Legal
- Shipping
- Marketing



An easy grid guide can be very helpful in determining what areas need to be assessed and who should be on the team.

A complete and sound impact assessment is critical to protecting the patient!



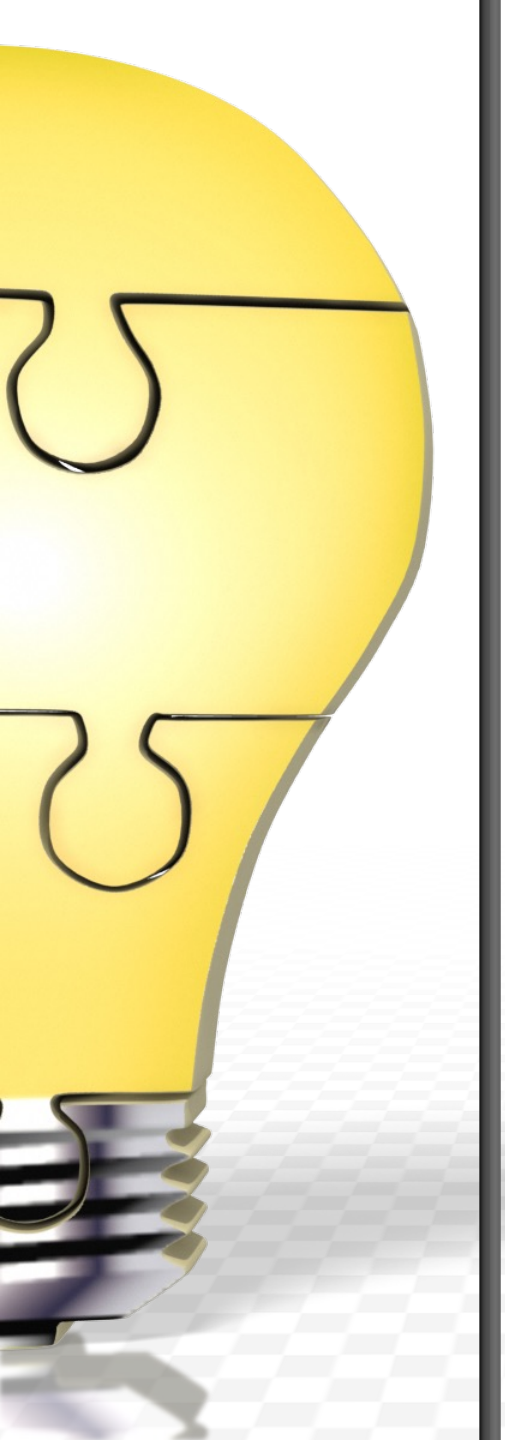
Impact Assessment

Every change requires an assessment of the impact of the change!!!!

For every area the team decides may be impacted, objective evidence is needed that the change did no harm.

Additional studies, such as development, validation, stability, or testing to ensure that the product still meets it's release specifications or intended use may be needed.

Part 2

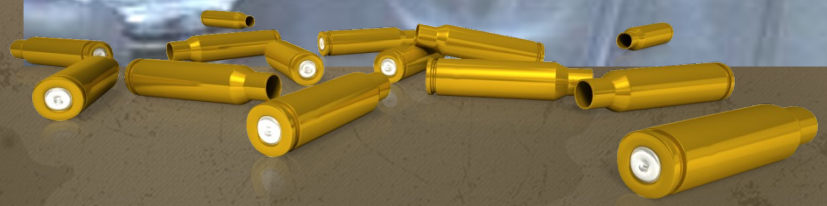


Providing Detail in the Change Control

History

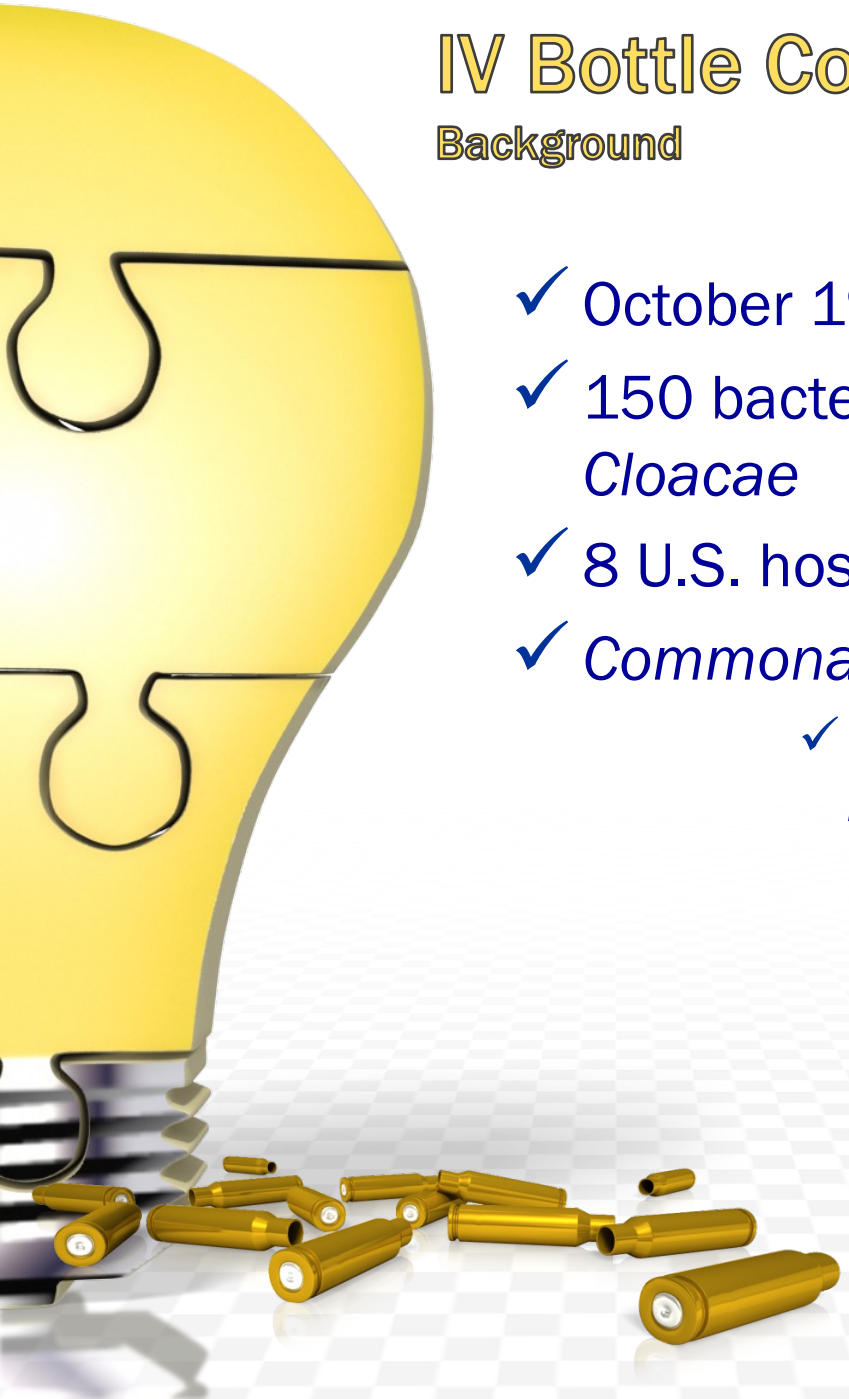
CASE #1

IV Bottle Contamination



IV Bottle Contamination Case

Background



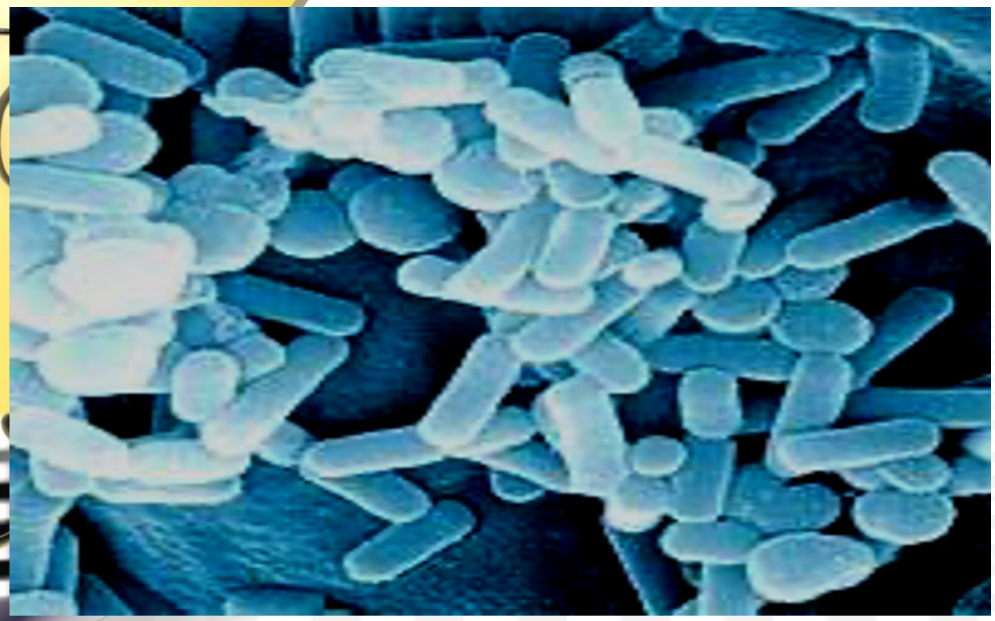
- ✓ October 1970 – March 1, 1971
- ✓ 150 bacteremias caused by *Enterobacter Cloacae*
- ✓ 8 U.S. hospitals
- ✓ *Commonality Observed*
  - ✓ *– All used fluids and IV systems manufactured by Abbott Laboratories*

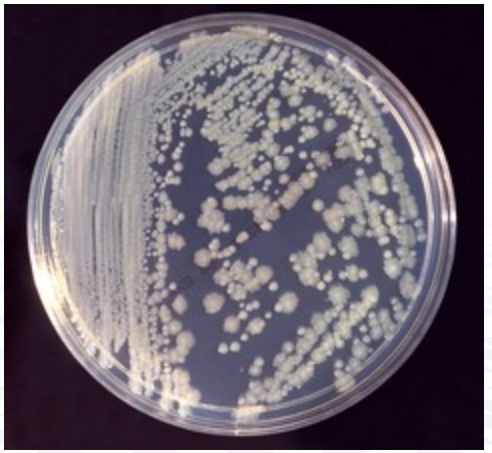
IV Bottle Contamination Case

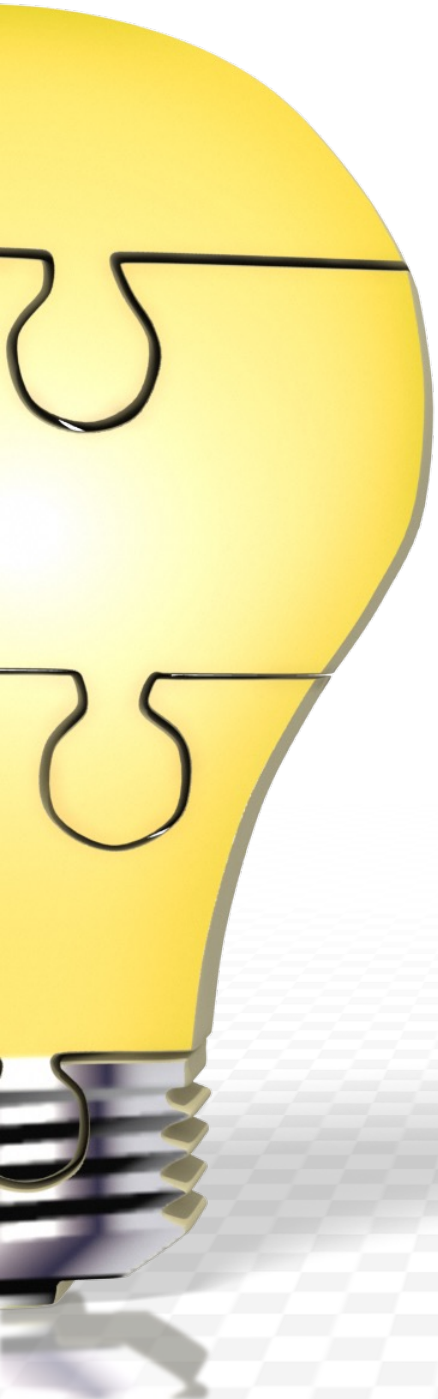
Background

Enterobacter Cloacae

- ✓ Gram-Negative Organism
- ✓ A relatively common “ICU bug”
- ✓ Opportunistic pathogen among the vulnerable (i.e. infants and the elderly)







Abbott Laboratories

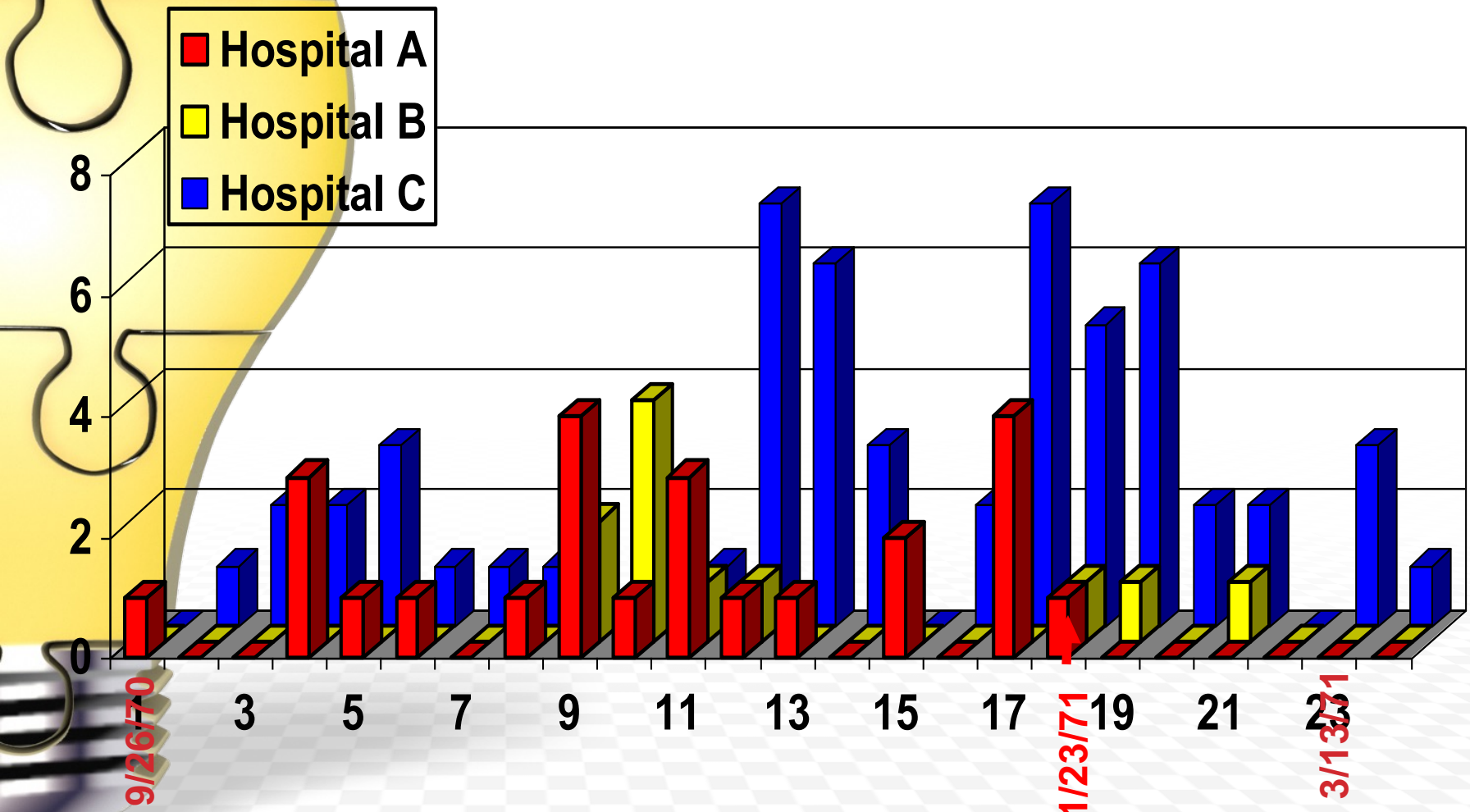
Company Background 1970

- ✓ A Diversified Company:
  - Consumer Goods (Selsun®, Murine®, Similac®) 1960's
  - Hospital Products (Monitors, IV Equipment, Drug Testing).
- ✓ **Cyclamate = 30% of Revenue**
- ✓ **Largest Supplier of IV Fluid in U.S.**
  - 45% Marketshare

Abbott
A Promise for Life

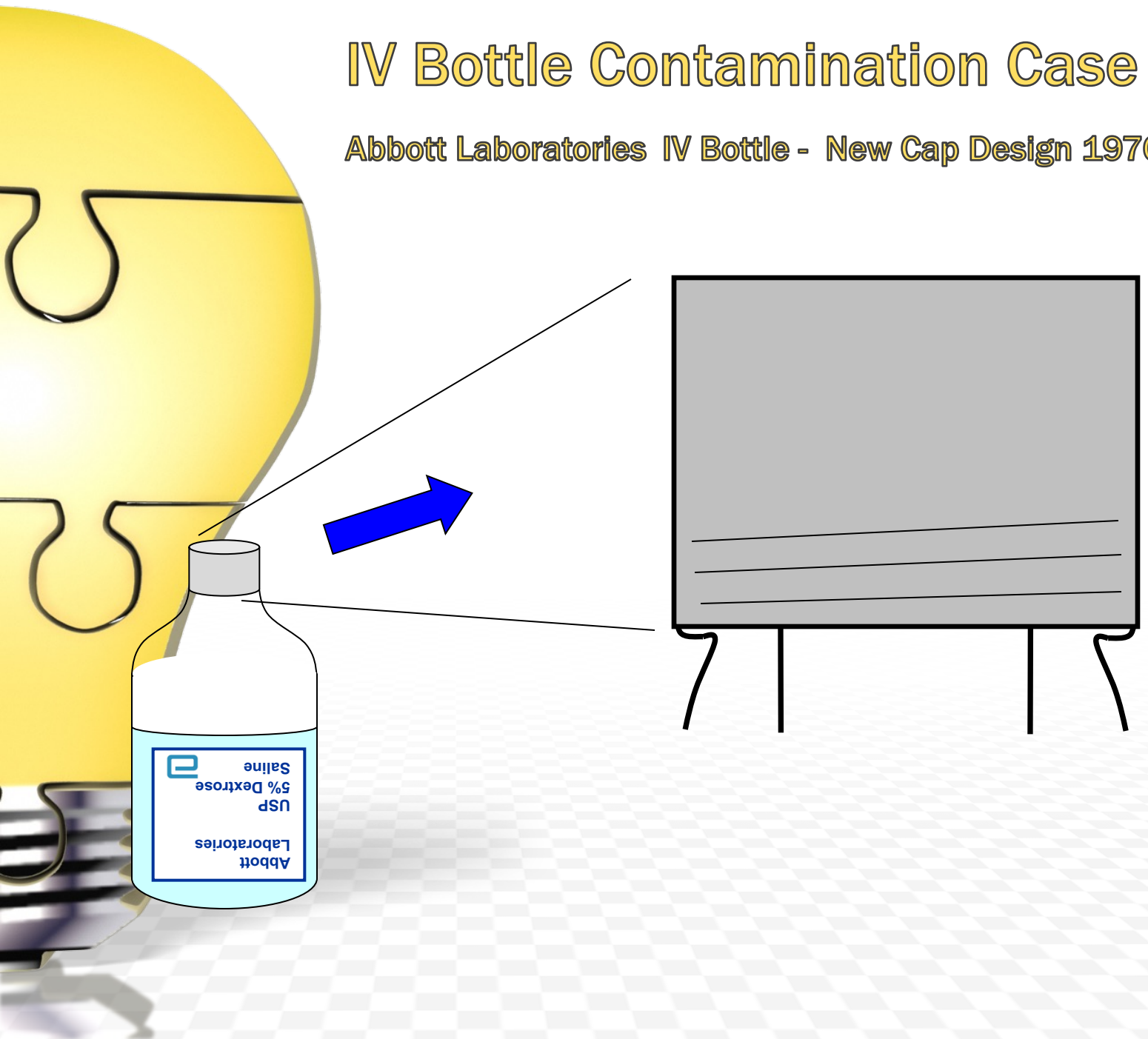
IV Bottle Contamination Case

IV-Associated Septicemias 1970-1971



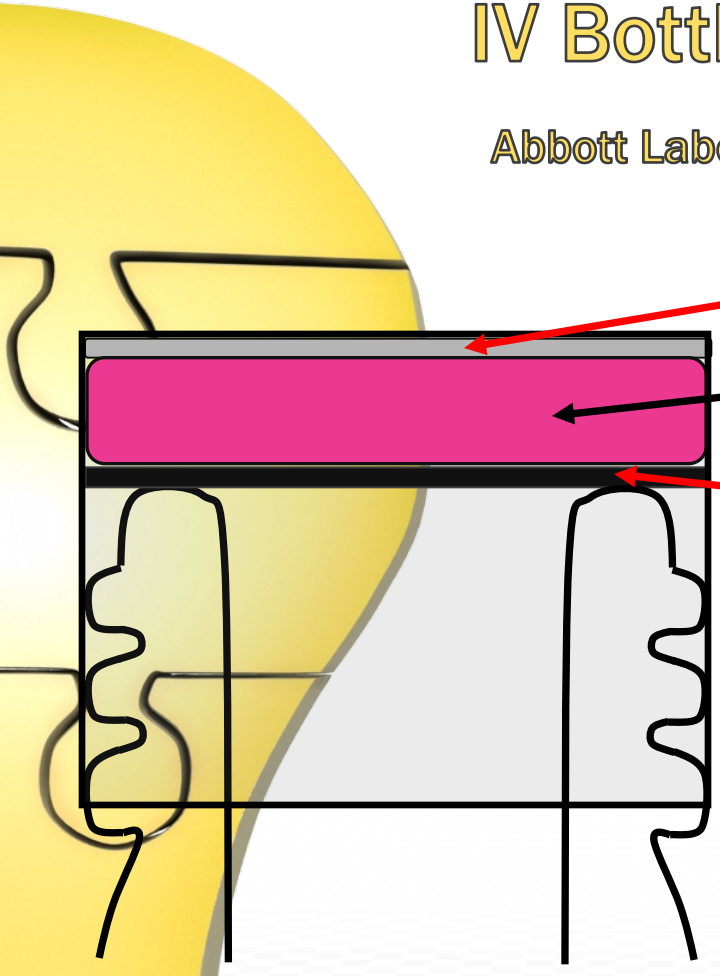
IV Bottle Contamination Case

Abbott Laboratories IV Bottle - New Cap Design 1970

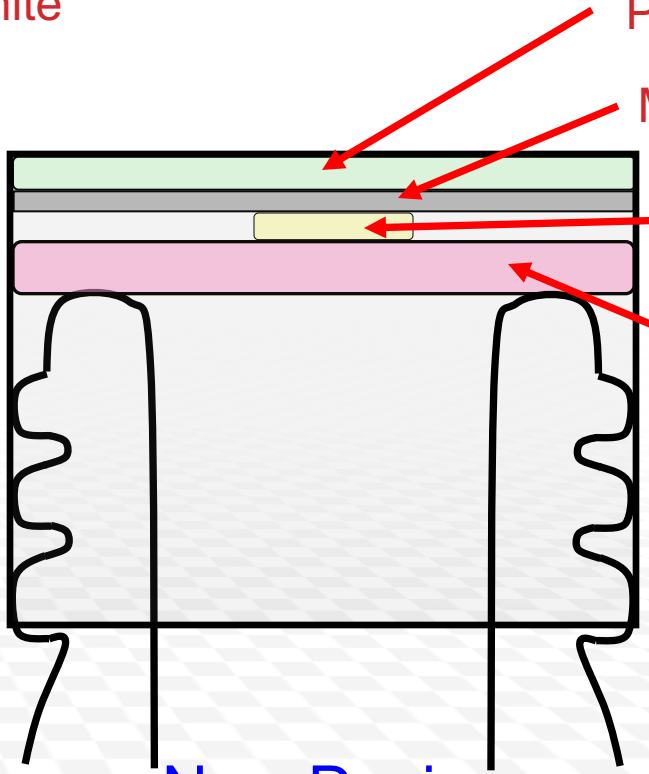


IV Bottle Contamination Case

Abbott Laboratories IV Bottle - New Cap Design 1970



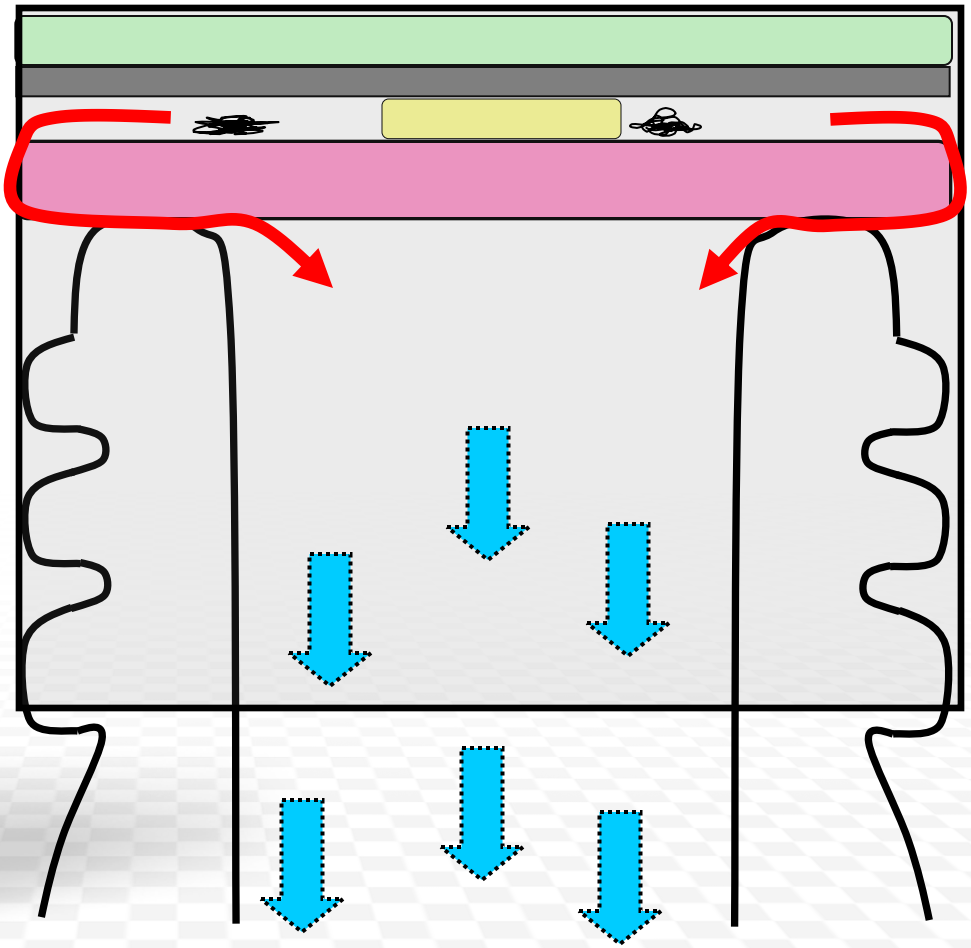
Old Design

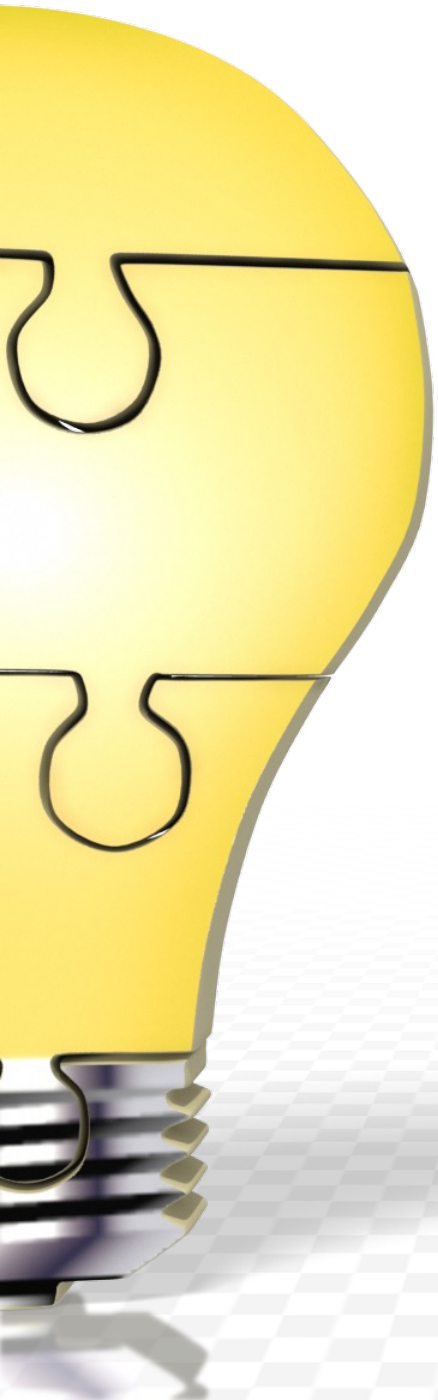


New Design

IV Bottle Contamination Case

Contamination Intrusion





IV Bottle Contamination Case

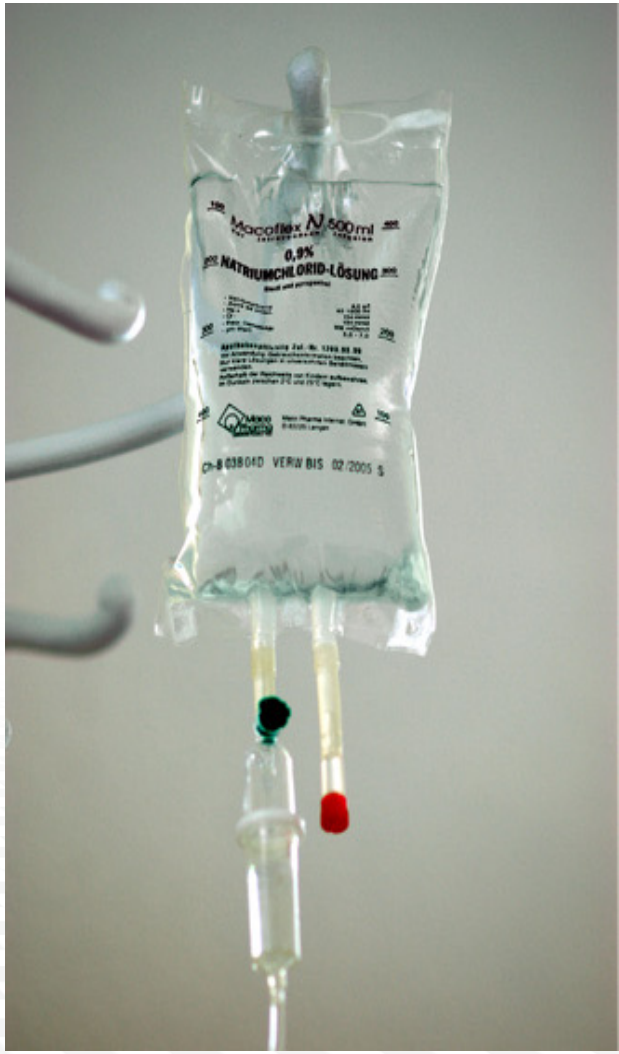
Outcome

- ✓ Contaminated Bottles linked to:
  - >434 Infections
  - 49 Deaths
- ✓ Abbott forced to recall 3.5 million bottles of IV fluid
- ✓ IV Sales Decrease 84% ($17.9 million to $3 million)
- ✓ Abbott redesigns IV bottle seals
- ✓ Litigation Ensues

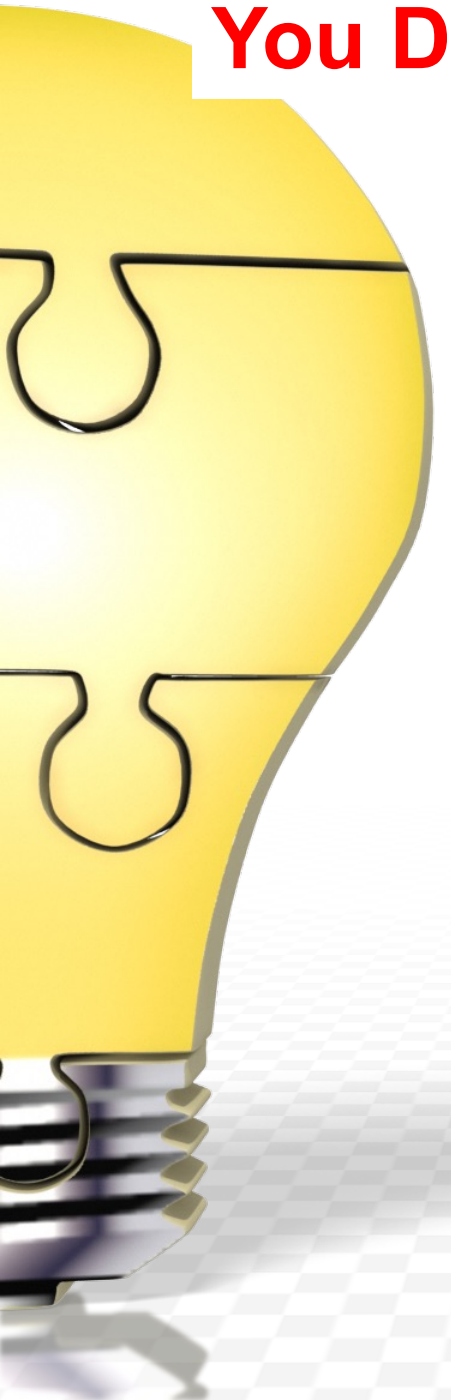
IV Bottle Contamination Case

Investigation Findings and Recommendations

- ✓ Abbott Laboratories:
  - Facility Cleanup
  - Screw Cap Inadequate
  - Spun off IV Business
- ✓ Hospital Procedures:
  - ~24 hr Changeout
  - Minimize IV Integrity Breach
  - Avoid Disrupting Contents
  - Never Replace Cap



You Don’t Know What you Don’t Know!!



IV Bottle Contamination Case

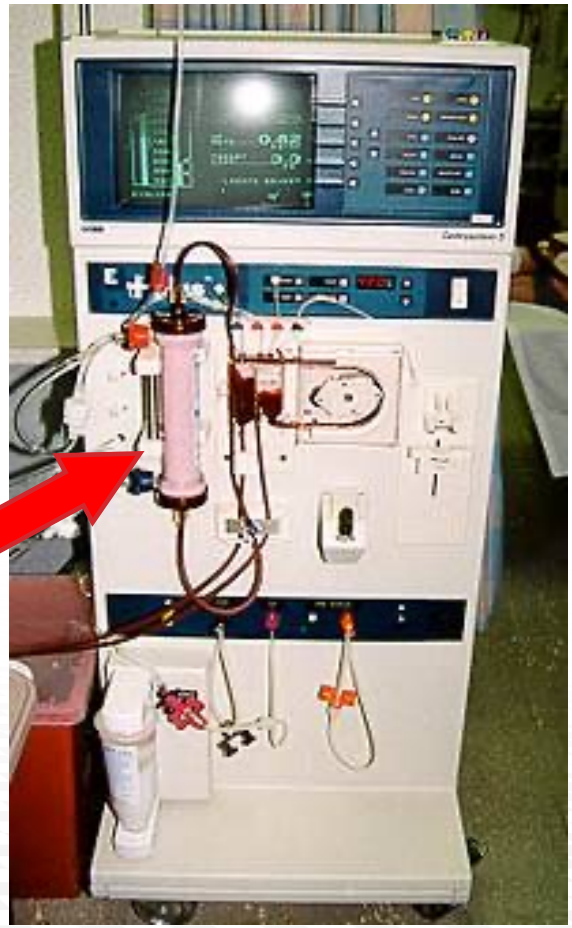
- ✓ *What can we learn?*
  - ✓ *Importance of Detailed Change Control*
- ✓ *How does Validation Help?*
  - ✓ *Sterilization Validation*
  - ✓ *Container Closure Validation*

Hemodialysis Filter Case

Hemodialysis Filter Case Timeline

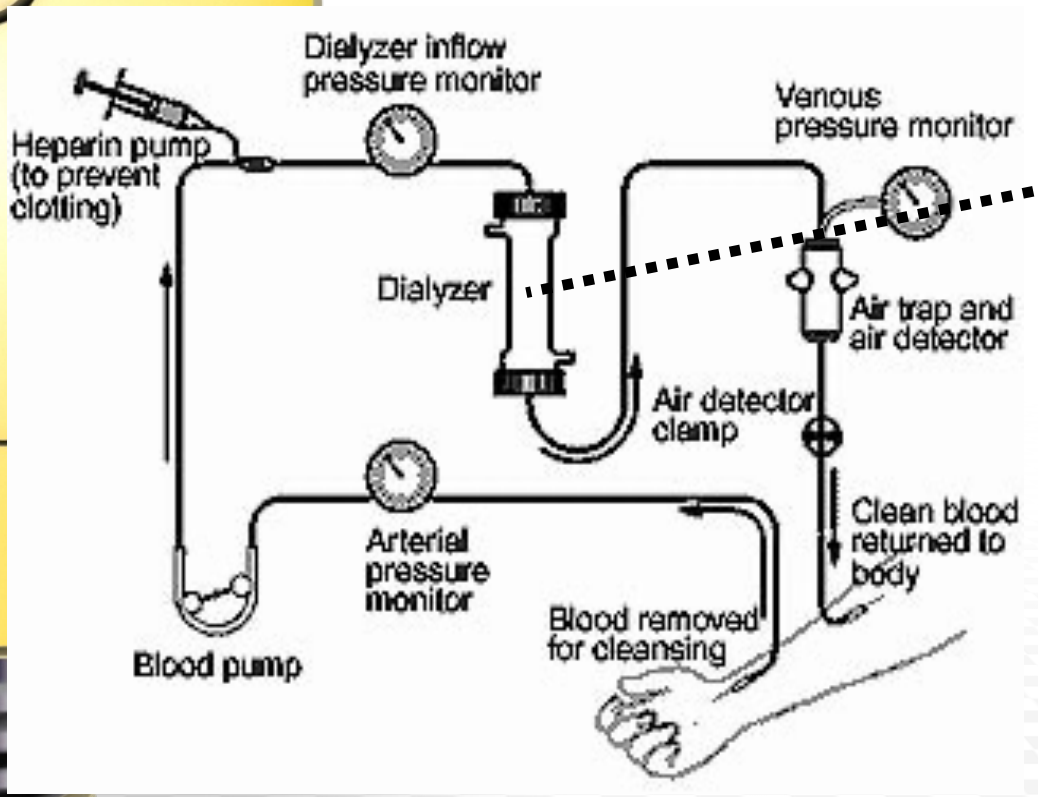
<u>August 2001</u>

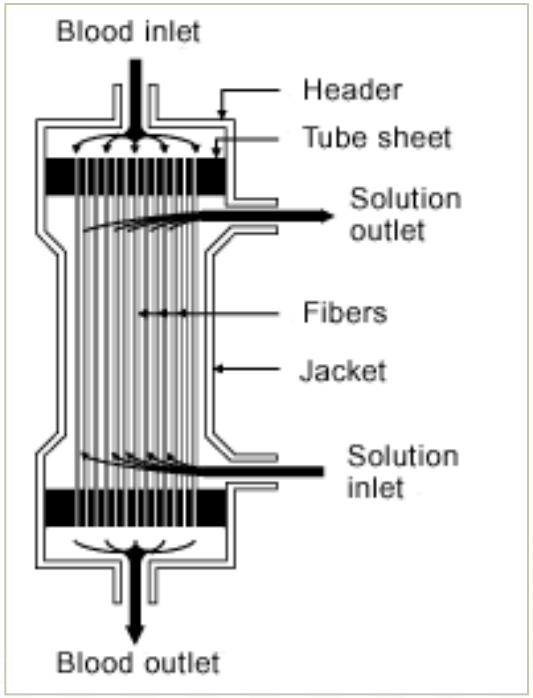
- ✓ Dialysis Patient Deaths - Spain
- ✓ Cardiac Arrest; 15 min – 7 hrs
- ✓ 21- 35 age range
- ✓ Gas bubbles in blood



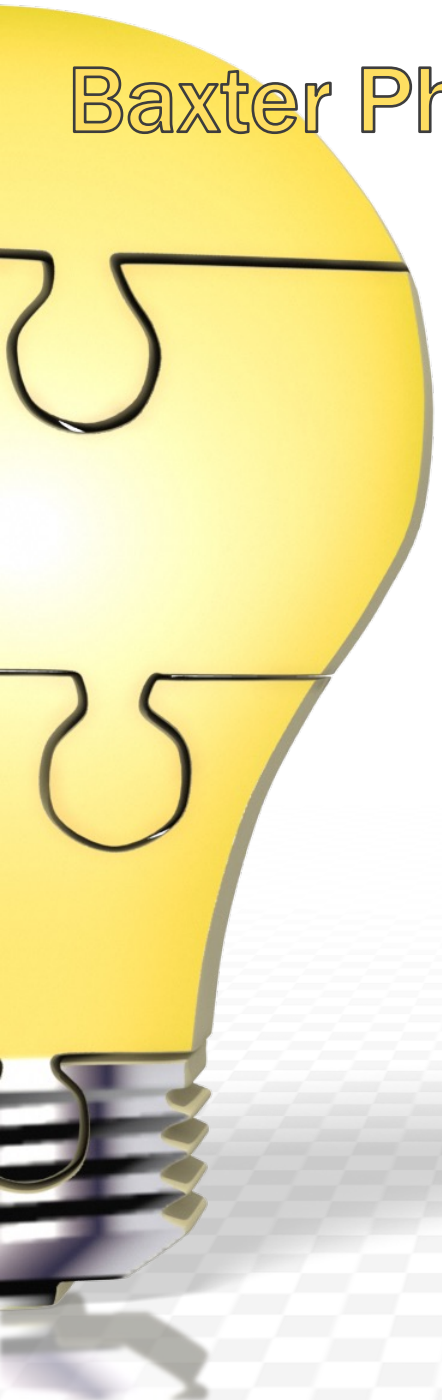
Hemodialysis Filter Case

Althane™ A, AF, AX dialysis filters





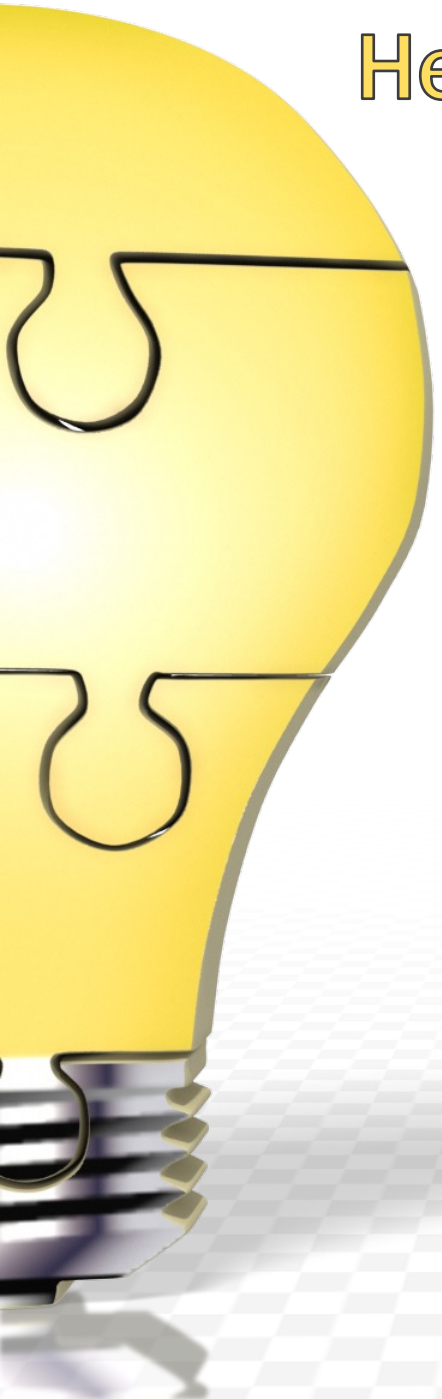
Baxter Pharmaceuticals Background Information - 2001



- ✓ Large hospital supply/medical product company
- ✓ 45,000 employees
- ✓ Mfg & Sales in 110 countries
- ✓ $ 6.9 Billion in annual revenue
- ✓ OEM Manufacturer
- ✓ Renal products ~20% of revenue

Baxter

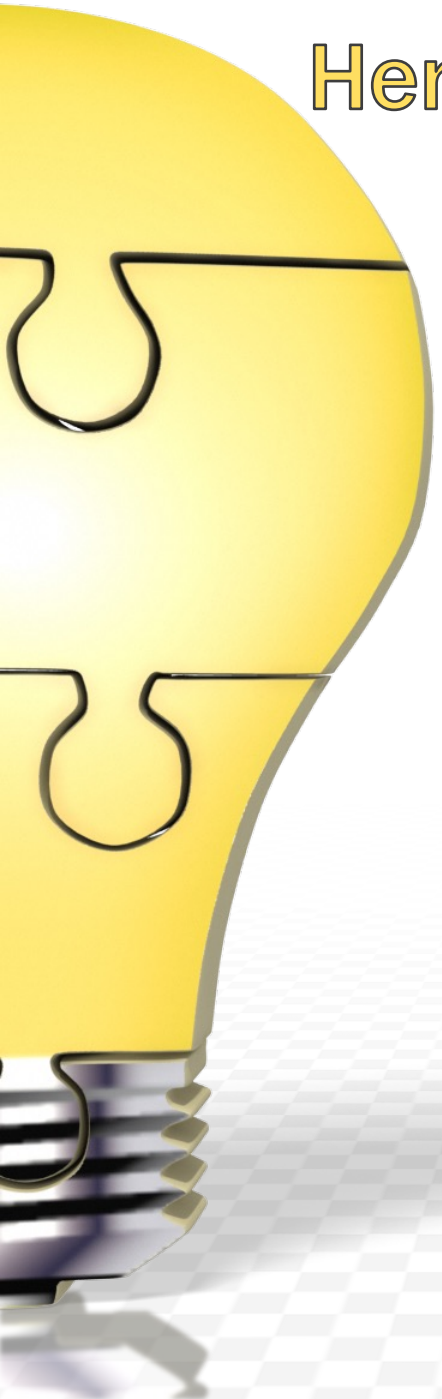
Hemodialysis Filter Case Timeline (cont.)



Aug-Sept 2001

- ✓ Baxter investigation exonerates filters
- ✓ Voluntary *Limited* Recall by Baxter

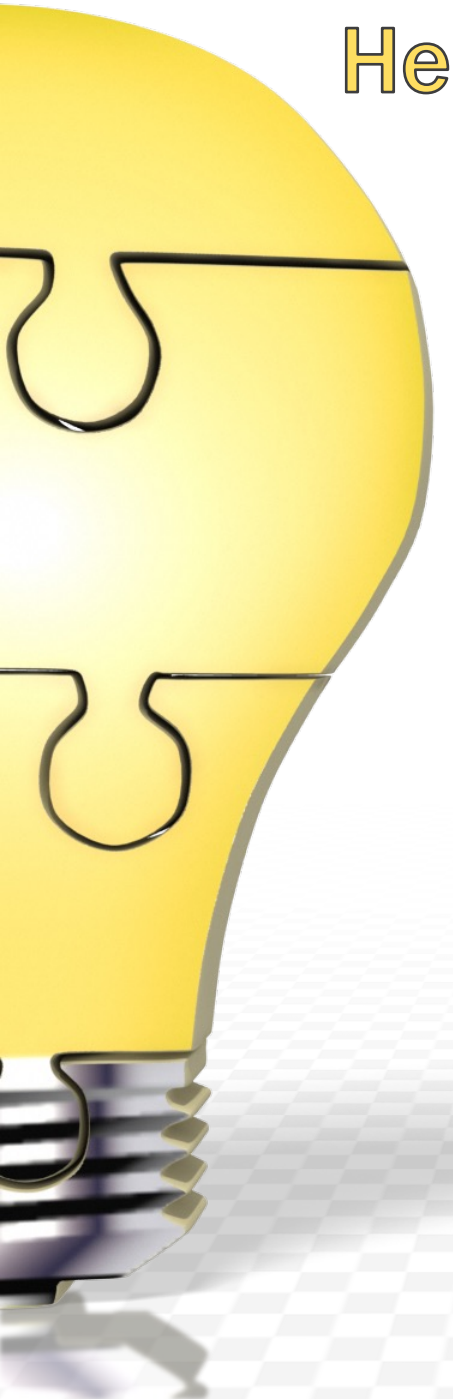
Hemodialysis Filter Case Timeline (cont.)



Oct 2001

- ✓ Croatia 23 Deaths
- ✓ Independent investigation exonerates filters
- ✓ JMS/Nikkoso Initiate Recall

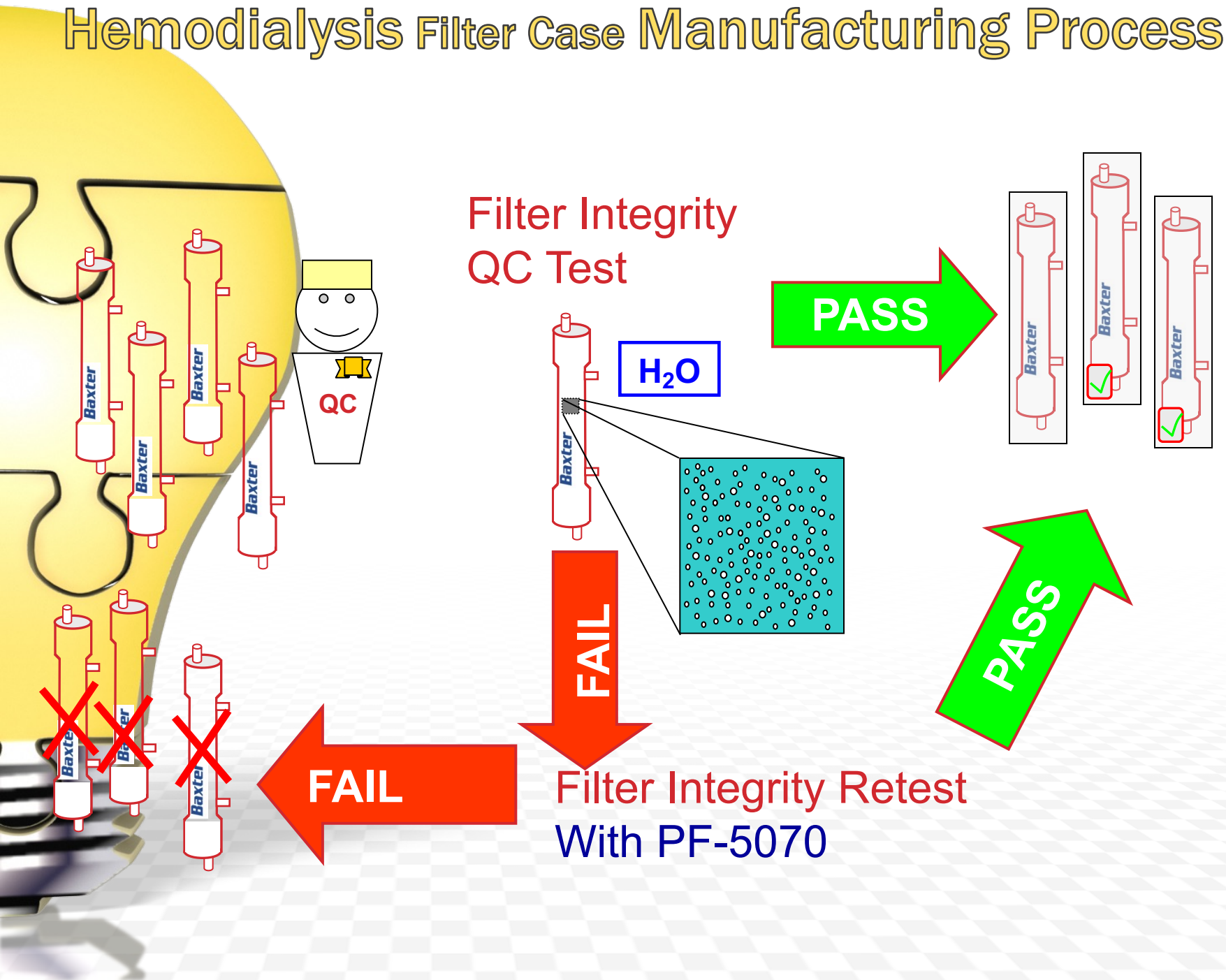
Hemodialysis Filter Case Timeline (cont.)

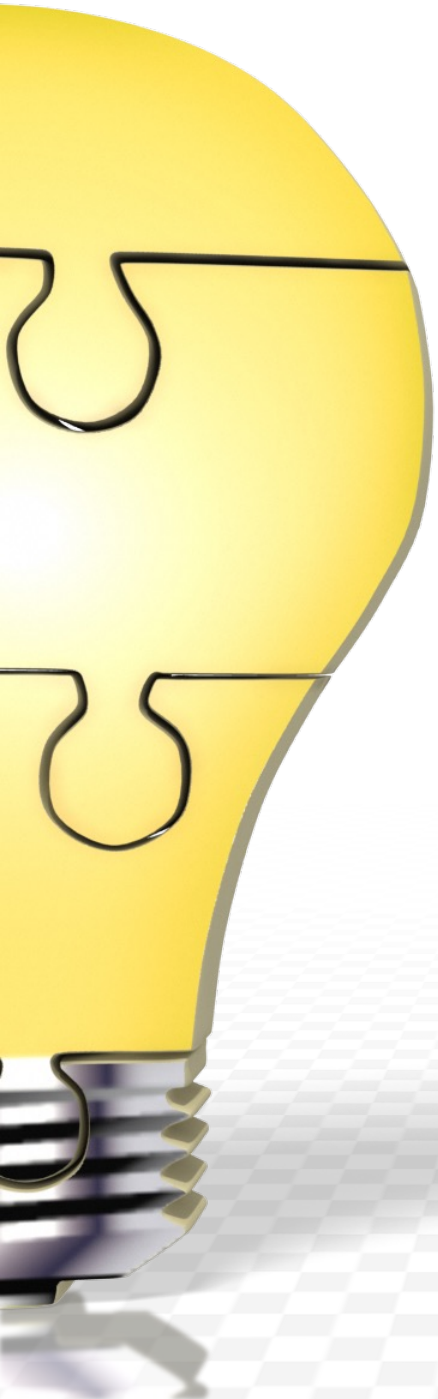


Oct-Nov 2001

- ✓ Deaths in Texas & Nebraska
- ✓ Worldwide Recall
- ✓ Investigation finds root cause

Hemodialysis Filter Case Manufacturing Process





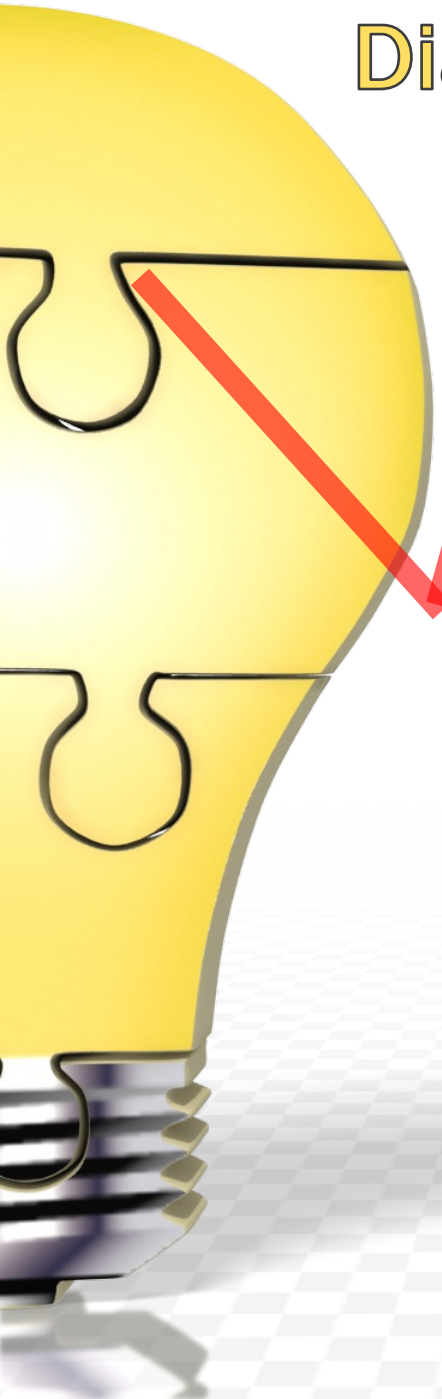
PF- 5070 Chemical Properties

- ✓ An Industrial Solvent
- ✓ Cooling/heat transfer/cleaning solution for electronic equipment
- ✓ Virtually non-toxic
- ✓ Fast evaporating
- ✓ 160 µL = fatal dose*

**Journal of the American Society of Nephrology* Study 2005

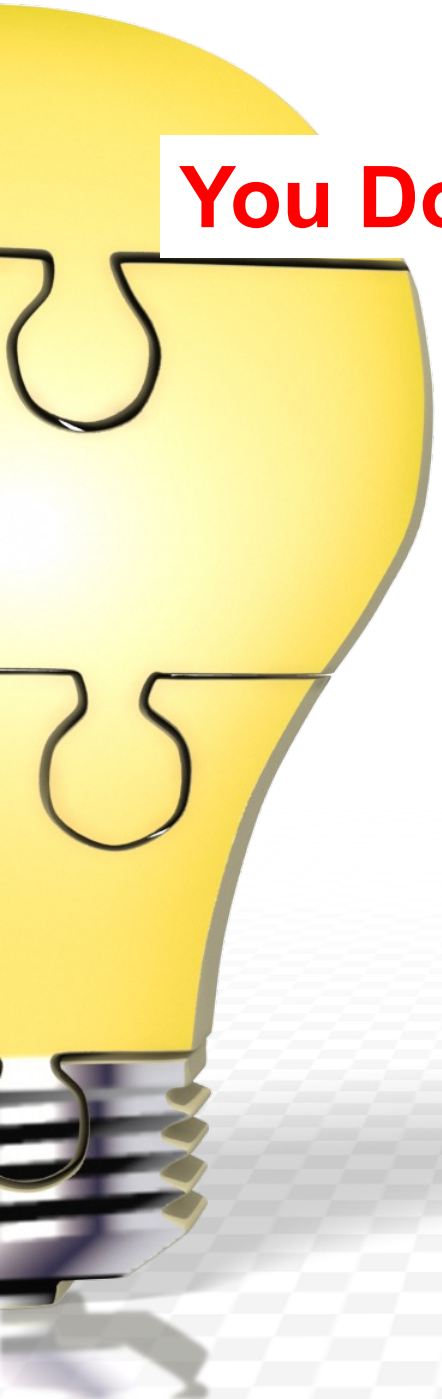
3M

Dialysis Filter Case Outcome



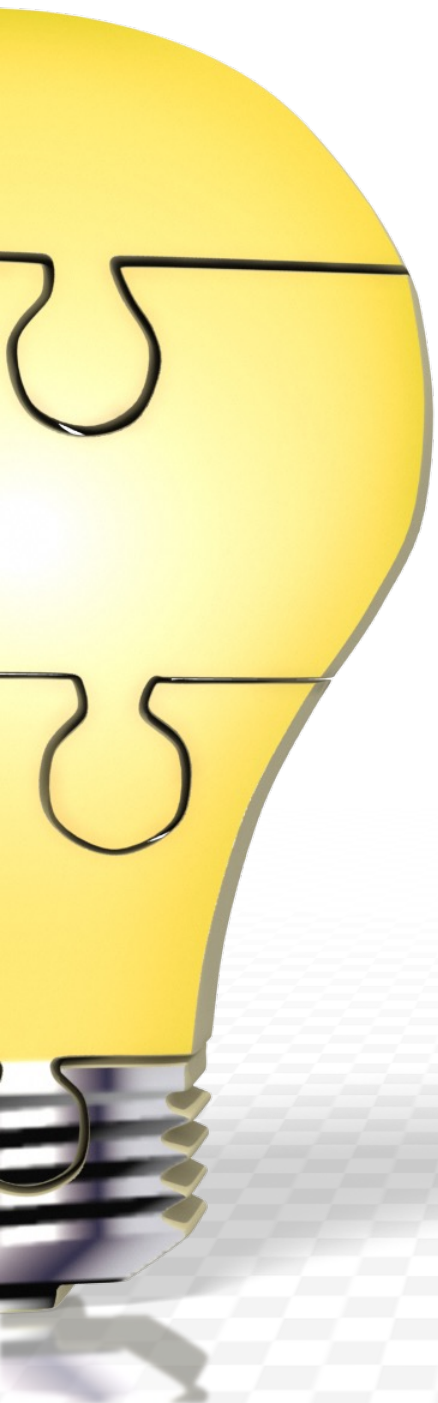
- ✓ Complete Recall of Althane™ filters
- ✓ 85 Confirmed Deaths
- ✓ 2 plants idled/closed
  - ✓ Ronneby Sweden
  - ✓ Miami Lakes, FLA
- ✓ 500 layoffs
- ✓ $150 million allocated to date for damages

Hemodialysis Filter Case



You Don’t Know What you Don’t Know!!

- ✓ *What can we learn?*
  - ✓ *Importance of Detailed Change Control*
- ✓ *How can Validation help?*
  - ✓ *Filter Cleaning validation and MAC Calculations*



Performing the Assessment

2.1 Review of Change Description – All Assessors

Each assessor must read the details of the CCR and the associated documents under Description tab and discuss the proposed change as needed with the CCL, SO, CM, other assessors, and/or project teams.

2.1.1 If it is determined that additional information is required to be added to the change description, the CCR shall be returned to allow this additional information to be added.

2.2 Assessment of the Change – All Assessors

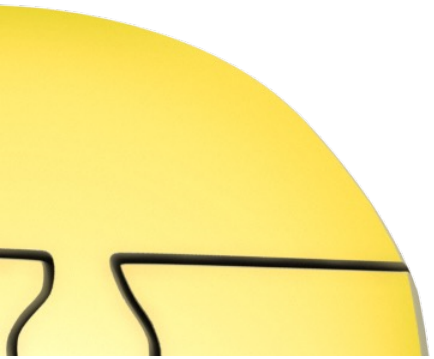
Each assessor is required to:

2.2.1 Analyze the potential impact of the change and document the impact (yes/no), rationale for impact and any deliverables required for the change. Reference any supporting documentation as needed and document the assessment as described in TOR-SWI-000491 "Instructions for the Use of Trackwise for Change Control" for Trackwise CCRs or TOR-SOP-001325 "Instructions for the Use of Phenix for Change Control" for Phenix CCRs.

2.2.2 Verify that all GMP documentation and/or systems, (including but not limited to Raw Material Specifications, Master Product Specifications, SOPs, BPRs, SWIs, Validation documentation, LIMS, SAP and Product Licenses), impacted by the change will be updated and aligned as part of the CCR.

2.2.3 Ensure deliverables are clearly listed and can be easily converted into action items within the plan. (i.e.: Instead of "Qualify equipment", indicate "Approved IOQ qualification protocol and IOQ Report")

2.2.4 If Impact? (Yes) is selected, indicate deliverables to be added to the action plan.

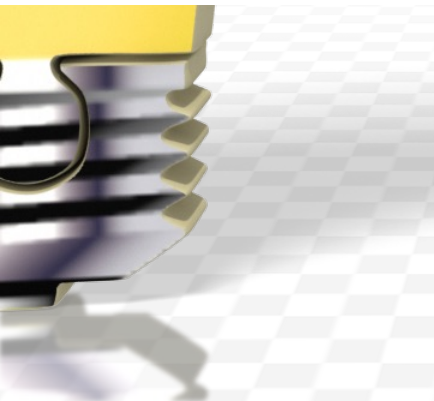


2.2.5 If Impact? (No) is selected, then a rationale must be included to indicate "Why" there is no impact to their area and no deliverables should be requested. **NOTE:** a rationale of "No (MTech, Validation, Quality or HSE) impact" would not be acceptable.

2.2.6 Identify any additional assessors/areas required to assess the change.

2.2.7 Assess any risks associated with the change and provide information to CCL.

2.2.8 Work with CCL to determine whether a Control Plan is required to monitor the effectiveness of the change post-implementation. If required, provide the parameters to be monitored and the conditions to complete the evaluation in the deliverables section. **NOTE:** Control Plan should be always considered in case of process parameter changes, changes to raw materials and changes in testing.



2.3 Manufacturing Technology Assessment of the Change

Performed by Manufacturing Technology Assessor with support of required SMEs from the Manufacturing Technology department.

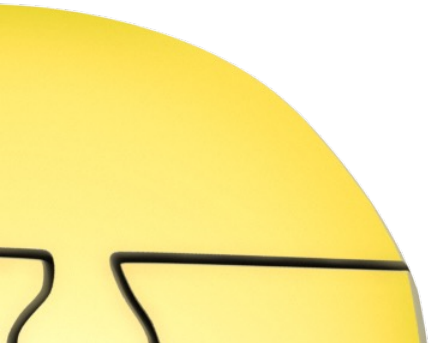
2.3.1 The Manufacturing Technology Assessor will determine the impact and provide the rationale for whether the proposed change is technically justified for each of the following:

2.3.1.1 Manufacturing Processes

- Bulk Manufacturing (e.g., process parameters, alert limits, process performance)
- Adsorption, Final Bulk, AlPO4 and Formulation (e.g., change in DS matrix)
- Filling and Inspection

2.3.1.2 Drug Substances and Drug Product Impact (SISPQ)

2.3.1.3 Cleaning Processes (e.g., change in clean or dirty hold time or cleaning methodology)



2.3.1.1.1 Detailed description for Cleaning Assessments is included in "Procedure for Performing Cleaning Validation Assessment".

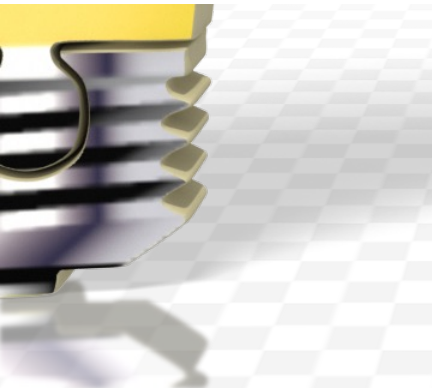
2.3.1.4 Raw materials including chemicals, consumables, and media (e.g., extractables and leachables studies)

2.3.1.5 Analytical methods (e.g., testing detection limit and testing matrix)

2.3.1.6 Seeds (raw material change or manufacturing of seed)

2.3.2 The Manufacturing Technology Assessor will also determine the impact of the proposed change on GMP systems managed by Manufacturing Technology and identify deliverables.

2.3.3 Deliverables shall include statements for each of the following:



2.3.3.1 SPC Program

- Update to SPC SOP or area specific SOP

2.3.3.2 Process Maps, CPP/CQA

- Update to Process Map to reflect new alert limits or tests

2.3.3.4 GMP Documents

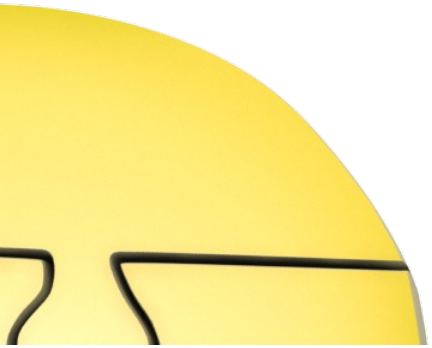
- Cleaning SOP updates
- GMP laboratory procedures

2.4 Quality Operations (QO) Assessment of the Change

Performed by QO Operational Quality, QO Sterility Assurance, or alternate quality representative as appropriate for the change, to determine whether change has a GMP impact and whether batches are impacted. Note: Additional Quality assignments/inputs may be required from Stability, Supplier Quality, Vendor Audits, GMP Compliance, Master Data and Product Quality.

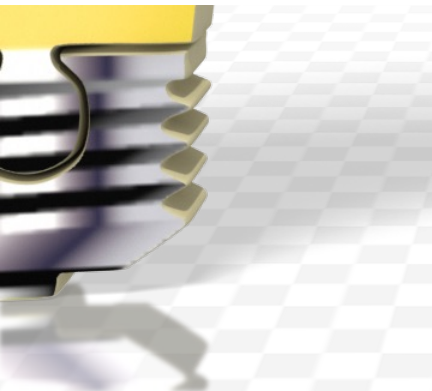
2.4.1 The QO Operational Quality Assessor will consider the impact on the following and identify required deliverables:

- Documentation
- External documentation (e.g. C of A)
- Labeling
- Ongoing stability programs
- Qualification/ agreement of a supplier
- Quality Systems
- Raw material (new materials, specifications, SAP, Supply Chain information)
- Reference data (e.g. SAP: changes to material description, storage conditions etc…)
- Product Stability (Requirements for new studies or changes to ongoing studies)
- LIMS (changes in test specifications, new STKs, test methods etc…)
- Product and Material Specifications
- Training



- Impact products where Sanofi Pasteur is the subcontractor
- Subcontracted products
- Organizational Impact
- Identify additional assessors to assess the change for stability, batch release (LRP) impact.
- Materials and/or batches requiring Quality Batch Tracking
- Reference/Retention samples for testing changes at the filled/labelled stage
- Whether a GMP Compliance Walkabout is required
  "Operational Quality GMP Compliance Walk-About Checklist".

2.4.2 When Quality Batch Tracking is required, the assessment will verify that the CCR material #s field lists the impacted materials and will include deliverables to:

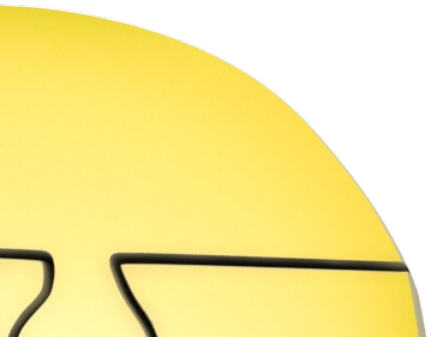


- Tag the impacted materials and/or batches with Quality Batch Tracking data as per TOR-SOP-000899.
- Remove the Quality Batch Tracking tag, if required, from the materials and update the tag for the batches upon closure of the CCR or associated Multi-part.

2.4.3 The QO SA assessor will consider the impact on the following and identify required deliverables:

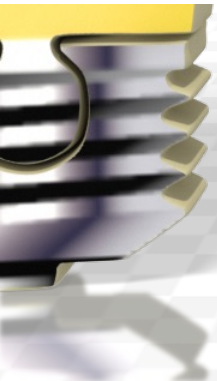
2.4.3.1 Utility related changes (for water, pure/clean steam, and compressed gases)

- Validation status (e.g. any intrusive work required, types of changes / modification)
- Routine monitoring program
- Documentation (e.g. SOPs, P&ID, MASTER templates, system #, etc.) and training
- Testing parameters and criteria
- Output quality of the water, pure/clean steam, and compressed gases
- Information flow
- System release requirements
- Adherence to current site and corporate policies and guidelines



2.4.3.2 Facility and environmental related changes

- Validation status of the facility (include HVAC)
- Routine environmental monitoring program (including MASTER and PharmNet Web database)
- Classified environments and aseptic conditions
- Equipment, materials and personnel flows
- Documentation (e.g. SOP, facility drawings, MASTER and PharmNet Web templates, facility / system #s, etc.)
- Training
- Cleaning and disinfection processes
- Adherence to current site and corporate policies and guideline



2.4.3.3 Aseptic Process Simulation Study

- Major facility renovations requiring facility shutdown/non GMP
- Major modifications to equipment or facility which may result in process change
- Major modification to equipment or facilities that can potentially affect air quality or airflow to the aseptic environment
- Increases in maximum number of production personnel
- Environmental monitoring results
- Change to process is outside of validated parameters
- Documentation
- Training

Note: changes regarding start-up of any new process or any major modification to GMP process or major building renovation must be assessed to determine whether an internal audit is to be conducted as per TOR-SOP-001408 (7).

2.5 QO Validation Assessment of the Change

Performed by QO Validation to determine whether the proposed change is expected to impact the current validated state of equipment, computer systems, processes, facilities, utilities, test methods and whether validation is required for the change.

2.5.1 Assessor will consider the impact on the following and identify required deliverables:

- Analytical/Methods, including TMV (indicate a requirement for concurrent TMV as a Multi-Part in the plan)
- Aseptic Processing
- Calibration/ Certification
- Computerized Systems
- Decontamination
- Equipment
- Facilities
- Time Out of Refrigeration
- Process
- Shipping
- Sterilization

- Storage
- Utilities
- Cleaning
- Container Closure System

2.5.2 In addition, QO Validation assessor will determine whether the proposed change will impact the validation status of the computerized systems supported by ITS.

2.5.3 Assessor will consider the impact on the following and identify required deliverables:

- Identify business areas or processes impacted
- Identify the impacted platforms and impact to qualification of infrastructure, including WiFi infrastructure
- Impact regarding the Validation dossier (i.e. Product Release, Batch Records, etc.)
- Impact on the system availability, security, data integrity and the data traceability
- Training requirements for this change (e.g., update to training modules / end user training)
- Key documentation to be created or to be updated (User Requirements, Specifications, SOP, Hand-Off package, DRP document, etc.)

- Requirement for special preparations for Go Live or for Rollback (Redundant infrastructure, Rollback action plan, Data archiving, etc.)
- Downtime planned and impact on business users
- Identify all potential risks associated with this change (data loss, backup / production failures).
- Documents attached for further analysis

2.5.4 SAP Master Data Compliance Group

SAP Master Data Compliance will determine whether the proposed change is expected to impact SAP Master Data in accordance with TOR-SOP-005827.

2.6 HSE Assessment of the Change

Performed by HSE Department to determine whether the proposed change is expected to impact safety, security, environment, or ergonomics of personnel. Refer to TOR-SOP-000590.

2.6.1 Assessor will consider the impact on the following and identify required deliverables:

- Environmental impact
- Impact on ergonomics
- Impact on safety of personnel
- Impact on security
- Regulatory impact on HSE

2.7 Regulatory Affairs Assessment of the Change in Trackwise

2.7.1 RA completes the assessment within TrackWise for the ICC and RA sections.

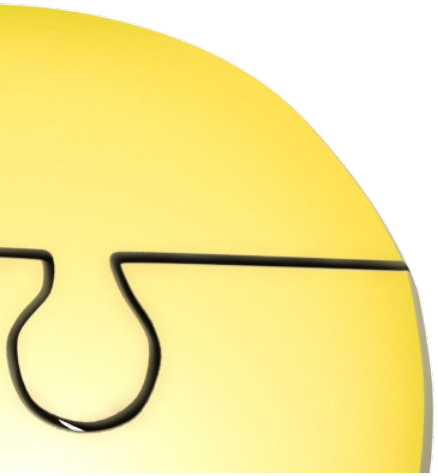
2.7.2 RA Assessor confirms that the list of products in the "Potential Product Impacted" field is accurate. If there is potential regulatory impact "ALL TOR PRODUCTS" should be updated to list all the applicable TOR products. Request the CCL or Change Management to correct the list as appropriate.

2.7.3 RA Assessor determines if the change has potential CMC submission impact through review of the Regulatory Guidances.

2.7.4 If there is no impact, enter "No" in the "ICC" Impact Field. Document the rationale for no impact in the "ICC" Specify Rationale Field. Enter "Not Required" in the RA Assessment Field.

2.7.5 If there is impact, enter "Yes" in the "ICC" Impact Field and enter the name of the RA Assessor in the RA Assessor Field.

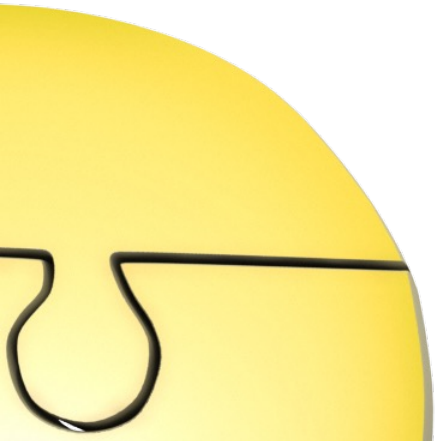
2.7.6 Note that in some situations, the impact on the quality of the process/product might require review of other assessments (Manufacturing Technology and Validation Compliance); in these situations, the RA Assessor will have to consult with those assessors before completing the RA assessment.



2.7.7 Enter “Completed” in the “ICC” Evaluation State field, once the assessment has been finalized.

2.7.8 RA Assessor evaluates the proposed change, to determine the regulatory impact and to record the reporting category.

2.7.9 If there is no RA impact, enter “No” in the RA Impact Field. Document the rationale for no impact in the RA Specify Rationale Field.



2.7.10 If there is impact, enter "Yes" in the RA Impact Field and provide rationale for license impact in the RA Specify Rationale Field citing specific regulations and guidance documents.

2.7.11 Document the regulatory assessment for product licenses impacted by the change in the RA Specify Rationale and RA Deliverables as appropriate.

2.7.12 Enter "Completed" in the RA Evaluation State field, once the RA assessment has been finalized.

2.9 Additional Assessments

2.9.1 Depending on the nature of the CCR, additional assessment may be performed but not limited to the following areas: Stability, ITS, QO Vendor Audit, Technical Services and Cleaning and Sterilization Groups.

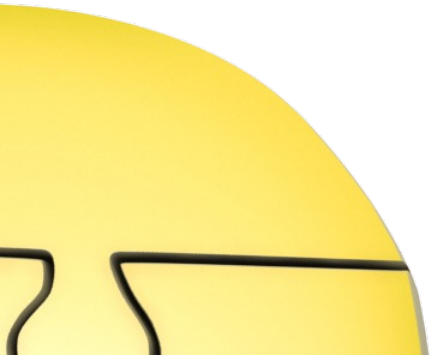
2.9.2 **Stability**

2.9.3 Assessor will consider the impact on the following and identify required deliverables:

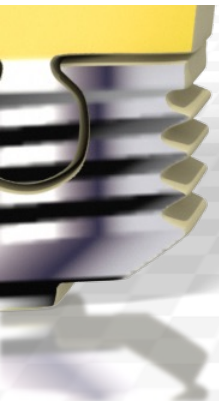
- Stability Protocols, including adding/deleting new test, changes in test SOP, changes in acceptance criteria and shelf life/expiry dates for any market
- LIMS master data, including changes in testing specifications, changes in test SOP, changes in STK
- Requirement for new studies to support the change (validation lots, accelerated testing)
- Routine monitoring program change as a result of a new presentation, new components, etc.

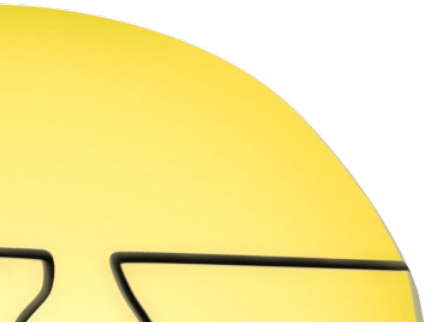
2.9.4 **QO Supplier Quality group**

2.9.5 Assessor will consider the impact on the following and identify required deliverables:



- Material Name, SAP code (applies to quality managed materials that are tested by QC)
- Supply chain of the material being provided (Distributor, Manufacturer (full address))
- Updates to "Approved Vendor List" based on the supply chain information
- Material Specifications
- Full address and details of service for the service providers
- Approved Vendor List (for vendors, not listed on the "Approved Vendor List", an evaluation of the quality systems via physical audit or questionnaire is required)
- Quality Agreements



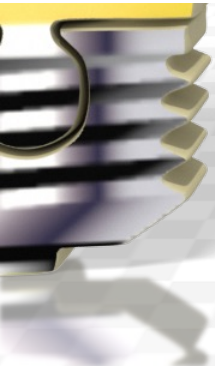


2.9.6 **Technical Services**

Performed by Technical Services Assessor to determine whether the proposed change will impact the Commissioning and Qualification status of the equipment and facilities.

2.9.7 Assessor will consider the impact on the following and identify required deliverables:

- Change in any equipment or critical part of equipment
- Facility design layout
- Utility (any change in water system, HVAC system)
- Commissioning status of the equipment/facilities
- Qualification status of the equipment/facilities
- Prodige Master Drawings
- BAS/FMS



2.9.8 **Sterilization Group**

Performed by Sterilization Assessors to determine whether the proposed change will impact the sterilization status of the equipment.

2.9.9 Assessor will consider the impact on the following and identify required deliverables:

- Equipment: modification in size, material of construction, configuration, process operation
- Product or raw material: composition, concentration
- Process activities where equipment is used
- Introduction of the new equipment, new method of sterilization
- Introduction of comparable sterilization methods within the manufacturing area
- eInfotree updates

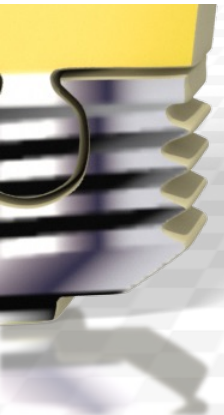
Detailed description for Sterilization Assessments is included in TOR-SOP-004360 “Procedure for the assessment of changes to validated sterilization, decontamination or depyrogenation loads”.

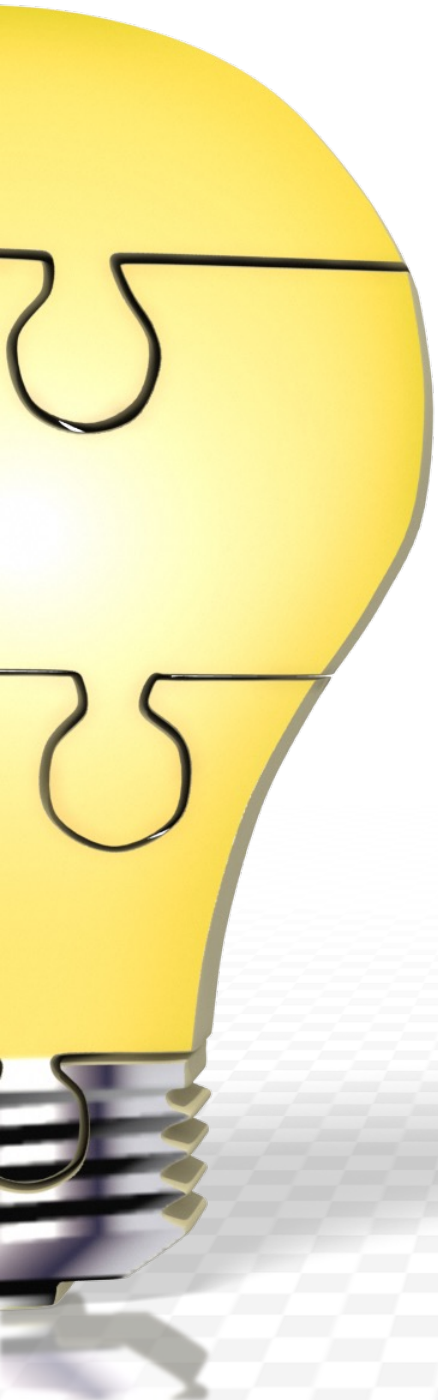
2.9.10 Product Quality (Batch Disposition) and Quality Planning Group

Performed by Product Quality / Quality Planning Group to determine whether the change will impact batch disposition and planning.

2.9.11 Assessor will consider the impact on the following and identify required deliverables:

- Lot Release Protocol (LRP), new Master LRP Template
- CBER submission requirements
- Communication to BGTD, NIBSC, ANSM, PEI and other international regulatory agencies
- Material numbers
- Impact on the inter-site release process/documentation
- Product Specifications





Thorough Assessments from multiple functions are necessary to protect patient safety

Questions? Comments?

Questions?

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