

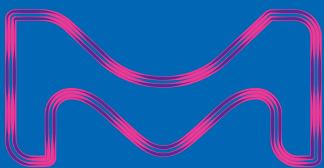
Millipore®

Filtration, Separation
& Preparation

The Science of Managing Change for Filters*

In a world where change is inevitable, we minimize the impact to your critical manufacturing process by following a thoughtful, step-by-step approach to change controls.

*Bioprocess Filters: Aervent®, Biomax®, Clarigard®, Clarisolve®, Durapore®, Fortis®, Millidisk®, Milligard®, Millipak®, Millipore Express®, Millistak+®, Opticap®, OptiScale®, Optiseal®, Pellicon®, Polygard®, Retropore®, Ultracel®, Viresolve®, Lifegard™, Polysep™, Prostak™, Solvex™



The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

MILLIPORE
SIGMA

In today's biopharmaceutical industry, changes are bound to happen. As a result, suppliers must have a change control process in place to minimize disruption and enable customers to continuously comply with regulatory authorities and guidelines.

We are committed to controlling, managing and communicating changes in the most stringent manner to ensure security of your supply.

In executing a consistent process for change controls, our goal is to:

- Alleviate any potential concerns you may have regarding changes
- Provide you with accurate information when you need it
- Demonstrate equivalence, whenever possible, to expedite your risk-based assessment of a change, e.g., provide documented evidence that there are no adverse effects and product performs as it has in the past
- Reduce the level of effort and energy required on your part to accept the change
- Ensure regulatory compliance and product maintains a validated state

Ultimately, we strive to minimize the impact of any changes on your manufacturing process or drug product quality, safety and efficacy.

Change Control Process

Our worldwide change control process and supporting management procedures include the evaluation and assessment of a change, the development and execution of a qualification strategy, creation of robust customer change documentation, as well as the notification and implementation of change.

Why is a Change Control Process necessary?

A change is a modification to a product or process that may affect a physical or chemical property outside the limits of normal variability, or has the probability to influence product specification(s) or performance for the specific intended use of the product; in essence, a modification that may have a potential impact on your process, drug product, procedures or documents.

Changes occur in the biopharmaceutical industry because drug product life cycles often exceed the life cycles of raw materials, consumables and equipment used to manufacture them. Supply chains of suppliers are dynamic and constantly evolving; company’s product portfolios change, plants consolidate or manufacturing locations change, raw materials are discontinued, suppliers go out of business, regulatory authorities or EHS ban the use of certain materials, and more.

Regulatory Guidelines

Due to these changes, suppliers to the biopharmaceutical industry must have a change control process in place to minimize disruption and enable customers to continuously comply with regulatory authorities and guidelines.

Document	Guidelines
“ICH Harmonized Tripartite Guideline, Pharmaceutical Quality System Q10” (step 4 June, 2008)	<ol style="list-style-type: none"> 1. Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. 2. 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.
USP Draft Chapter <1083> Good Distribution Practices – Supply Chain Integrity	<ol style="list-style-type: none"> 3. Establish procedures for corrective actions when a product does not meet specifications, when the importer’s requirements are not met, or when there are changes in the supplier’s business.
WHO good distribution practices for pharmaceutical products Annex 5 from 2010	<ol style="list-style-type: none"> 4. Procedures should be established and maintained for the preparation, review, approval, use of and control of changes to all documents relating to the distribution process. Procedures must be in place for both internally generated documents and those from external sources.
EU Guideline: on Good Distribution Practice of medicinal products for human use; (2013/C 343/01)	<ol style="list-style-type: none"> 5. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organization’s management and requires their leadership and active participation and should be supported by staff commitment. 6. A change control system should be in place. This system should incorporate quality risk management principles, and be proportionate and effective.
International Pharmaceutical Excipients Council (IPEC) Certificate of Analysis guide for Pharmaceutical Excipients (USP <1080> Bulk Pharmaceutical Excipients — Certificate of Analysis)	<ol style="list-style-type: none"> 7. The minimum number of lots to be fully tested for all specification parameters after a change has been made depends on the process and the significance of the change and should be based on sound statistical considerations. 8. Significant Change — any change that alters an excipient’s physical or chemical property from the norm or that is likely to alter the excipient’s performance in the dosage form.
EU Falsified Medicines Directive (Directive 2011/62/EU)	<ol style="list-style-type: none"> 9. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.

Table 1. Regulatory and industry guidelines that reference change.

Types of Change

There are two different types of change:

1. Changes that we may initiate in order to improve a product or a process, streamline production or to optimize operations
2. Changes that are initiated by our suppliers

Levels of Change

Regardless of who initiates the change, we classify changes into two levels:

1. **Notifiable** – A change that has a high probability of affecting a physical or chemical property outside the limits of normal variability, or has a high probability of influencing product specification or performance for the specified intended use. Such a change will require customer notification.
2. **Not notifiable** – A change that has a low probability of affecting a physical or chemical property outside the limits of normal variability, or has low probability of influencing product specification or performance for the specified intended use. Such a change may not require customer notification.

Examples of notifiable changes include, but are not limited to:

- Changes in manufacturing process steps that impact product specifications
- Change in raw material that impacts product specifications
- Change in animal derived components that impacts compliance
- Change in primary packaging

Examples of not notifiable changes include, but are not limited to:

- Change in secondary packaging
- Like-for-like changes in test equipment

Change Control / Qualification Process

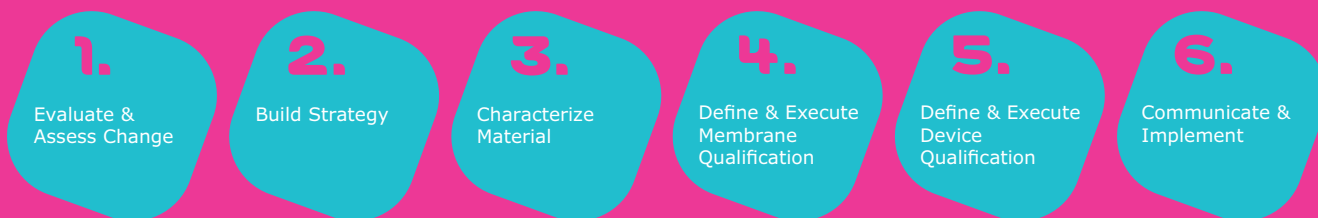


Figure 1. Shows a high level overview of the steps we take to control, manage and communicate changes.

1. 2. 3. 4. 5. 6.

Evaluate & Assess Change

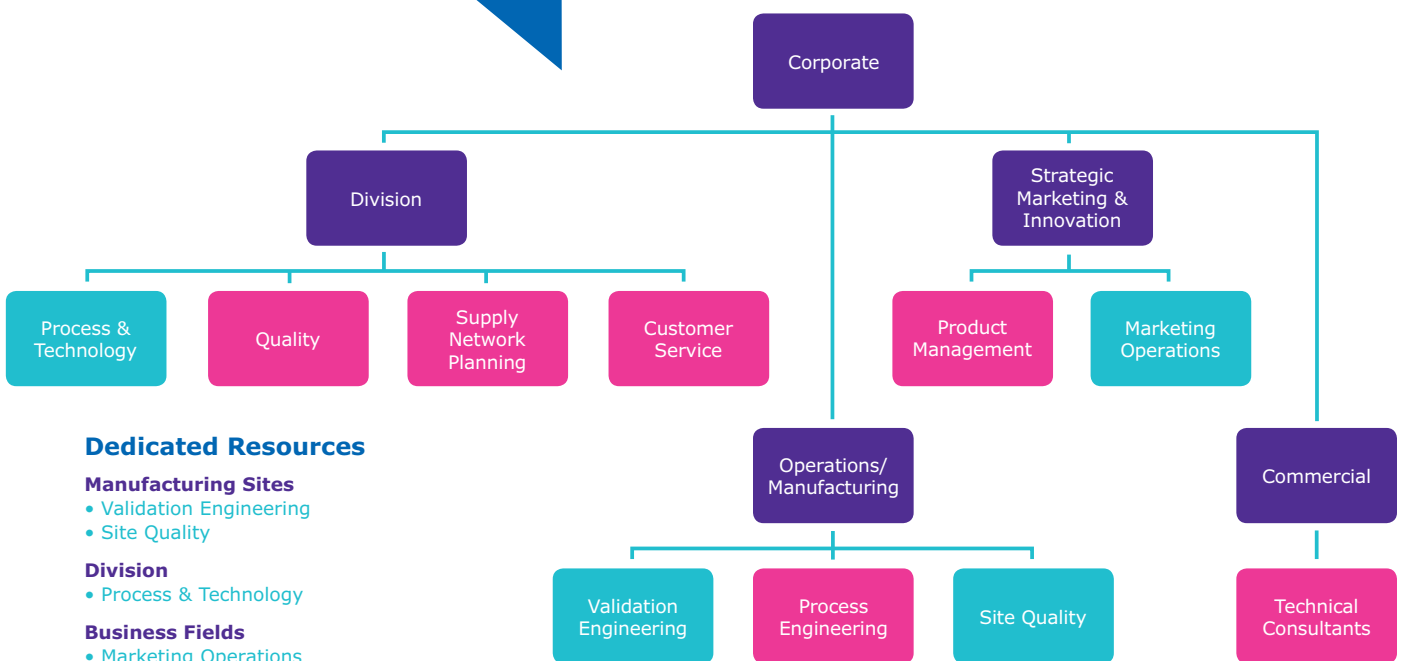
Our change control process begins with the assembling of a cross-functional change control team who evaluates and assesses the change. There are dedicated resources (*Process & Technology, Quality, Validation Engineering, Marketing Operations and Technical Consultants*) at almost every level of the organization (*Division, Operations, Business Unit and Commercial Organization*) to ensure that the change control process is followed.

The team evaluates the scope and impact of the change to the business, product line, application/ intended use, and ultimately, the customer.

Any potential risks associated with the qualification of the changed material in the manufacturing process are identified by the team. Areas of focus include quality of the product and impacted raw materials, manufacturability, claims and specifications of affected products, product validation criteria and changes to extractables and leachables profile. The team assesses the risks in terms of potential for occurrence, severity of issue, and ability to detect, and documents them in a Risk Assessment (RA). Mitigating actions for a selection of products and product attributes are determined for risk priority number's (RPNs) greater than a certain value. The RA is a live document which is revisited throughout the change control process and is updated accordingly. Based on the evaluation and assessment, the team follows a standard operating procedure (SOP) to determine if/when a change is customer notifiable and reviews Quality Agreements to determine if/when there are contractual obligations to notify.

If a change is associated with a critical raw material, the level of complexity and effort, as well as the amount of time to qualify the change is higher than other changes. For these notifiable changes, the team will estimate the run out the current raw material based on the short-term forecast and long range demand plan of a product, make a decision to buy a surplus of the current critical raw material and decide on when to notify customers of the change. The goal is to provide customers with 6-12 months notification of a notifiable change.

- ? Does the product require customer validation?
- ? Is the product classified as a Critical Quality Attribute (CQA) by our customers?
- ? Is the change associated with a critical raw material which comes into contact with a customer's drug product?
- ? How much time does a customer need to perform a risk-based assessment and accept the change?



- Dedicated Resources**
- Manufacturing Sites**
 - Validation Engineering
 - Site Quality
 - Division**
 - Process & Technology
 - Business Fields**
 - Marketing Operations



Build Strategy

The second step requires the team to build the strategy and document the project plan for qualifying and implementing the change. The plan encompasses the results from the RA, as well as documents:

- Description of the change
- Reason for the change
- Products affected
- Manufacturing sites impacted
- Qualification approach
 - Tests to be re-done as part of the qualification, as well as the rationale for those tests
 - Associated protocols and the selected components/products to be tested and which other products they represent
- Success/acceptance criteria
 - For routine key lot release criteria, a historic comparison of PQ results is made
 - For non-routine test criteria, a head-to-head comparison of PQ results to pre-change controls is made
- Customer notification strategy
- Customer Summary Reports (CSRs)/data package
- Implementation requirements
- Timelines
- Action item owners

The result of the second step is an overall change control project plan, including a validation master plan and timeline, as well as an official change control. All of the tasks associated with the change control are opened and tracked via our change management system, Trackwise. If a change is a notifiable change and has been deemed customer notifiable, a pre-notification letter of the change, which includes a CSR of the validation master plan may be sent to customers and leveraged to solicit input on the plan.

Notification

- Optional Customer Pre-Notification Letter with Executive Summary of the Validation Master Plan





1. 2. 3. 4. 5. 6.

Characterize Material

The third step in the change control process is to select and characterize a new raw material. This is an iterative process broken down into three steps to identify a new raw material and/or a new source. We search for a new raw material based on a specification of required chemical and physical properties. We evaluate the feasibility of the new raw material through characterization and comparison to the current raw material. We select a new source/supplier only if necessary and go through our Supplier Quality Management process.

Material characterization includes the evaluation and comparison of the physical and chemical properties, as well as the biocompatibility effect, of the changed material.

To evaluate changes in physical and chemical properties, several analytical techniques (FTIR, H-NMR, GPC, TGA, DSC, ICPOES) are used to characterize chemical structures, impurities, molecular weights, decomposition and transition temperatures, metal content and more. The analysis of the new raw material is shared with customers in a Material Characterization Customer Summary Report (CSR) and used to assess the potential impact of the change on the manufacturing process.

To evaluate changes in the biocompatibility effect of the new raw material, several GLP biocompatibility studies on the affected component with the new raw material are performed to characterize the physiochemical, cytotoxicity, pyrogenicity attributes and more. The results of the component with the new raw material are shared with customers in a Biocompatibility CSR to provide documented evidence of no adverse biocompatibility effect from the change.

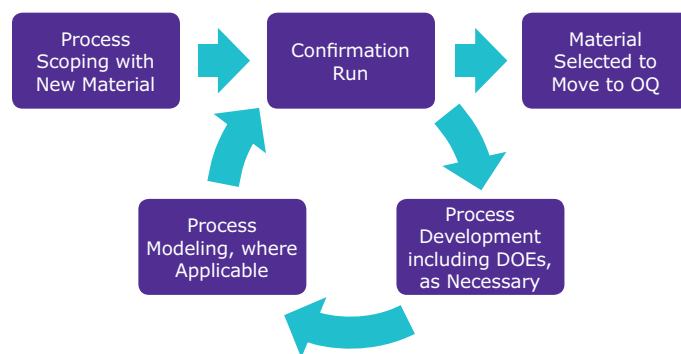


Figure 3. Select and Characterize New Raw Material

Customer Summary Reports

- Material Characterization
- Biocompatibility



Define & Execute Membrane/Device Qualification

Upon receipt of positive material characterization results, the fourth and/or fifth steps – depending upon the change – is to execute the qualification of the component and/or finished good product with the changed material.

1. Feasibility studies are performed to assess the need for process changes to accommodate the change in raw material.
2. To evaluate changes in potential organic contaminants, extractables testing of changed materials that come into contact with a customer's drug product (molded components, membrane, and support materials) is conducted to avoid interference

from other materials and provide the best comparison for the change. We generally extract 3 lots for 24 hours at ambient temperature using two analytical techniques (FTIR, RP-HPLC) and four different extraction solvents (water, alcohol, acid, base) to quantify levels of Non-volatile Residue (NVR) and Total Organic Carbon (TOC). We test to the ICH Q3D element list and focus on whether there are post-change species extracted or an associated increase in extractable levels. The results are shared with customers in an Extractables CSR to provide documented evidence of no adverse extractables performance impact from the change.

Membrane and Device Qualification

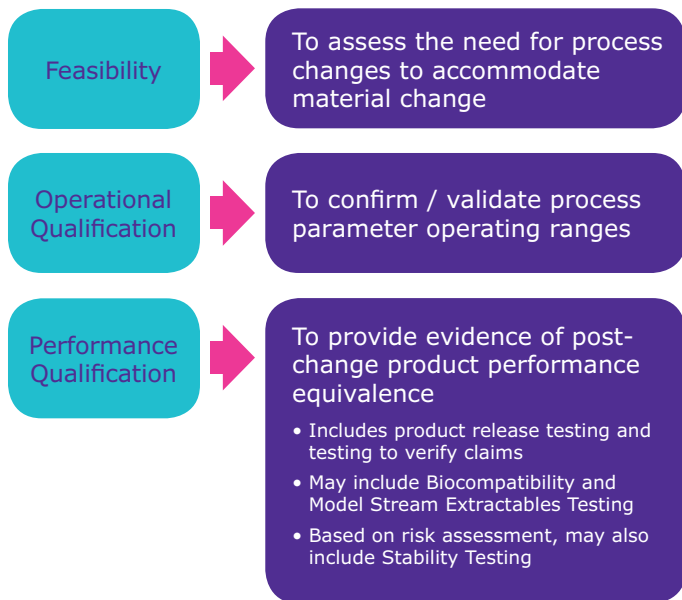
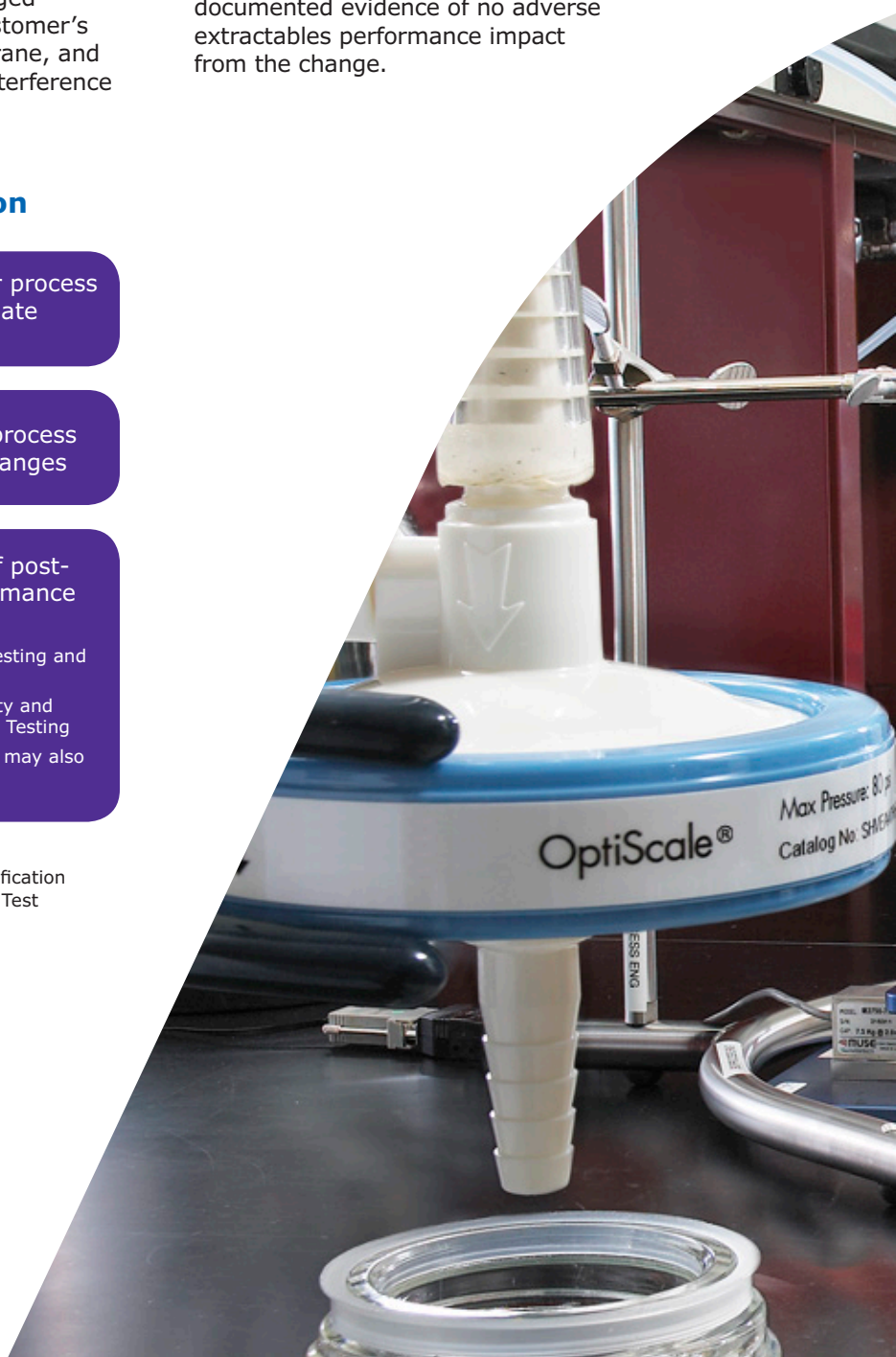


Figure 4. Definition and execution of the Operational Qualification (OQ), the Performance Qualification (PQ) and the Stability Test requirements for the affected membrane/device.



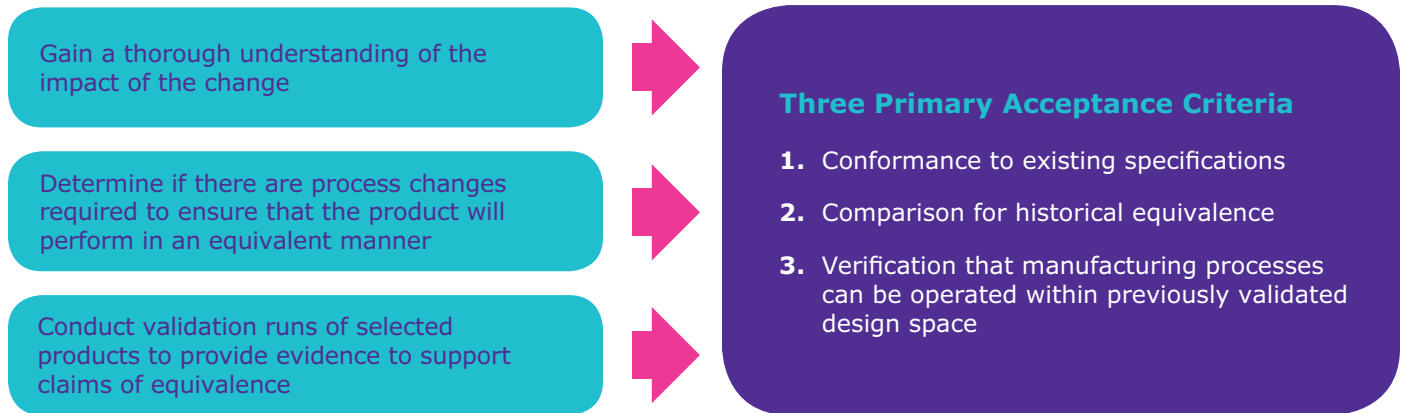
3. Operational Qualification (OQ) activities are conducted to confirm the operating ranges of the manufacturing process parameters and define the centerline conditions for Performance Qualification (PQ) activities.

4. Then, ≥ 3 PQ lots are selected to be tested for lot release criteria and to verify claims in validation guides. The results of the PQ are shared with customers in a Qualification CSR to provide evidence of post-change product performance equivalence.

5. Based on the RA, some products may be tested for stability. For product shelf-life, a minimum of 1 year equivalent accelerated aging is required prior to product shipment.



Change Control Process: Qualification Objectives



Historical Comparisons of Key Membrane Properties

1. Range of PQ results must fall within the historical range of released lots¹
2. Means of PQ results are within one standard deviation of the mean of historical distributions
3. Amount of predicted performance level overlap for the PQ and historical distributions
Target: $\geq 90\%$ Overlap

Note 1: Minimum of 20 historical lots over the most recent two (2) year time span.

Note 2: Failure to meet any of the above criteria requires assessment by subject matter experts and a full justification if acceptance is to be granted.

Finally, to further provide evidence that a post-change product will perform equivalently to a pre-change product, application studies that simulate typical customer application usage may be performed using relevant model streams. The results of this testing would be shared with customers in a Performance CSR.

Customer Summary Reports

- Extractables
- Membrane Performance Qualification
- Device Performance Qualification
- Application/Device Performance Data



Communicate & Implement

Part A: Communicate

Our worldwide change notification policy and supporting management procedures assure that our customers are notified of changes in a timely and consistent manner. One of the most effective tools in communicating changes is our change notification. Typically, a change notification is written by Marketing Operations; reviewed and approved by Quality and Product Management. The notification provides customers with a description of the change, reason for the change, the list of affected products / catalogue numbers, implementation dates, and any other relevant information, such as an Executive CSR of the Validation Master Plan or the actual test results of the changed material in the form of CSR's. Depending upon the change, samples may be made available to customers to assist in performing the risk-based assessment.

The approved change notification is submitted to Divisional Quality for distribution. Divisional Quality assigns a unique identification number to the change notification, and sends it to customers who have a Quality Agreement (QA) or Change Notification Commitment (CNC).

In addition to an external notification, there are numerous internal notification activities and documents, such as internal e-mail alerts, frequently asked questions documents, internal training and monthly change notification meetings, to ensure that worldwide Technical Consultant resources are capable of helping customers transition through the change. All of the external and internal change notification documentation is archived in a Divisional Quality database.

Part B: Implement

All changes require a robust implementation plan and timeframe that enables customers to assess the risk associated with a change and accept the changed material. The plan must also enable the manufacturing site to produce and ship products with pre-change and post-change material simultaneously and fulfill customer orders accurately.

A cross functional team consisting of Marketing Operations, Manufacturing Sites, Customer Service, and Supply Network Planning conducts a failure modes and effects analysis (FMEA) to identify all potential failure points in the supply chain ~ from order intake to production planning, production planning to distribution, distribution to customers. The team also takes into consideration the estimated run out date of the pre-change material to establish the optimal cutover date to begin shipping customer orders with the change material. Traceability of the changed material is built into the Enterprise Resource Planning (ERP) system via post-change part numbers for the Bill of Materials (BOM) and/or Lot Numbering System. When the change is finally implemented, customers are provided with last lot (pre-change) or first lot (post change) information.

Notification

- Customer Notification Letter with Customer Summary Report Availability
- Last/First Lot Information



To Place an Order or Receive Technical Assistance

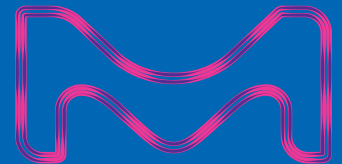
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