Standard for GEHC Life Sciences
Change Control process for
Designated products
1. Introduction

A process for change control is required for suppliers to the biopharmaceutical industry. As a supplier of products often used in a GMP environment, GE Healthcare Life Sciences (hereafter referred to as GE) acknowledges that change control is a critical process in the quality management system and necessary to fulfill the obligations to supply products with a consistent quality to our customers.

GE has adopted the principals of change notification best practices for single-use products, as described in “An Industry Proposal for Change Notification Practices for Single-Use Biomanufacturing Systems” BPOG/BPSA, BPI, May2017. GE applies similar principles to all product categories that are used in GMP environments, in a manner befitting the specific characteristics of the various product categories.

Changes to confidential unit operations will be informed of in a way that will not disclose IP or business critical information. More detailed information may be shared during audits.

2. Purpose

The purpose of this document is to provide an overview of the change control process for designated products within GE. Detailed procedures and instructions that are in compliance with this document are used at the local GE sites and can be reviewed during audits. This document may be used to introduce the GE Quality Management System to customers or other external organizations or individuals.
3. Scope

This standard applies to bioprocessing products, and cell and gene therapy products, that are available for subscription to change control notifications and thus are listed on the web page: [www.gelifesciences.com/rsf](http://www.gelifesciences.com/rsf).

This standard does not apply to Biacore™ products.

GE products within a FlexFactory™ platform are supported with change control notifications through individual product subscriptions, e.g. Xcellerex™ bioreactor bags, ReadyCircuit™ assemblies, etc.

Note that the ReadyToProcess columns packed with chromatography resins are supported with change control notifications through product subscriptions to the ReadyToProcess column and the included chromatography resin.

4. Definitions

**Change control:** Management of all planned changes associated with the design or manufacturing of marketed products.

**Product quality:** The product characteristics that are listed in the product specification.

**Critical subcontractor:** Contract manufacturer of critical raw material, product or process.

**Design changes:** Any modification to a product that may impact design form, fit or function.

**Product/process Contact Material (PCM):** The finished good that is in contact with the process fluid containing the medical product; also called wetted part.

**Form:** The unique and relevant physical characteristics of a part, defining the "look" of the part or item, e.g. shape, size, dimensions, colour, mass and/or other visual parameters which uniquely characterize and distinguish the part.

**Fit:** Fits intended application; The ability of a part to physically interface, connect with, or become an integral part of another part or assembly, includes for example tolerances. Whether the physical dimensions of a part fit into the product it was designed to go into. It must adhere to the specifications set by engineering in the design phase.

**Function:** The action(s) that an item is designed to perform, what the product actually does, product performance.

5. Steering principles

Each manufacturing unit has a change control board with relevant representatives from functions concerned with proposed changes. The representatives must be on an organizational level that gives authority to take decisions.

The board is responsible for:

- assessing all aspects of proposed changes
- assessing the output from risk management
- deciding on the extent of verification/validation
- deciding if a customer notification is required, see 7. Customer notification.
- reviewing and approving design and manufacturing changes
6. Risk Management of change

Changes are evaluated regarding product quality and customer impact from a risk perspective. The magnitude of this evaluation, proportionate with the magnitude or complexity of the change, may range from a brief discussion/handling to a full and comprehensive risk assessment. The risk assessment/customer impact assessment is documented.

When a potential risk is identified, measures are taken to reduce the risk to an acceptable level. Preventive measures are taken to minimize the potential impact on product quality/customer impact. Residual risk evaluation and overall risk acceptance are performed. Customer impact assessment will factor in heavily to the categorization of the change. Residual risk evaluation or overall risk acceptance may cause a proposed change to be abandoned.

7. Customer notification

For changes listed below in points 7.2-10, customers are always notified. For changes not listed in these sections, a notification may still be provided if the result of the risk assessment indicates an elevated risk (medium or high risk) associated with the change.

The listed points reflect customer input over many years, through many types of interactions (e.g. interaction regarding quality agreements, customer audits, customer feedback to notifications, interactions through industry organizations etc.), and are adopted to fit the different product area characteristics and needs.

The listed changes are not described in detail, as it is not possible to cover all the situations that may occur. Customer impact and criticality of a change is considered, and notification times may be adjusted to fit the nature and complexity of the change. An additional pre-notification is considered for significant changes.

For changes not listed in points 7.3-10, the result of the risk assessment will determine whether a notification is sent out. The decisions are taken by the change control boards. Notification time frames are based on the type of the change and the associated risks/customer impact. When the risk assessment and risk control process result is no-risk or low-risk impact on the quality of the product and customer impact, customers need not be notified of the change as an outcome of the risk assessment, and a notification of the change is only sent if the change is listed in sections 7.2-10.

7.1 Changes subject to customer notification, and time frames

Notification is given for products available for subscription to change control notifications listed on the web page www.gelifesciences.com/rsf, according to this Standard.

The time frames in sections 7.2 through 7.10 are an estimate that GE aims to fulfil. However, there may be extraordinary situations where GE may have to inform with shorter notice, and GE reserves the right to inform with shorter notice than described below.

7.2 Notification of changes concerning all product lines

Notification for the following changes will be sent minimum 3 months prior to implementation:

- New edition of this change control standard (in the unlikely event of GE reducing the stringency laid out in this document, a new edition of this change control standard will be notified minimum 6 months prior to implementation)
7.3 BioProcess chromatography resins, Density gradient media and Micro carriers

Changes for which GE will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk.

Changes for which notification is typically given prior to implementation:
- Change in label and primary packaging material
- Change concerning shelf life
- Change concerning storage conditions
- New edition of analytical specification, editorial changes

Changes for which notification is typically given a minimum of 6 months prior to implementation:
- Change of critical subcontractor
- Change of analytical specification limit within current limits
- Addition of a new test method
- Change regarding animal origin of raw material

Changes for which notification is typically given a minimum of 9 months prior to implementation:
- Change to a different test method
- Change of analytical specification limit outside current limits
- Elimination of test method
- Change of manufacturing site
- Change to a different raw material
- Change to manufacturing equipment or process – significant changes (that impacts product quality or performance) *

* If parallel manufacturing is not possible (pre/after-change), supporting data will be provided no later than at the time of implementation.
7.4 Standard cell culture media products

Changes for which GE will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk.

Changes for which notification is given 1 month prior to implementation:
- Changes in packaging
- Change concerning shelf life – if extending shelf life
- Change concerning storage conditions – if within currently validated range

Changes for which notification is given 3 months prior to implementation:
- Change to label and certificate content (removal of information)
- Change in product contact surface during manufacturing process
- Addition of new raw material manufacturer
- Change in specific product release testing
- Change of content to finished product specifications which affect the form, fit or function of finished products

Changes for which notification is given a minimum of 6 months prior to implementation:
- Change of critical subcontractor (manufacturing, finished product release testing, irradiation contractor)
- Change of test method for finished product release test
- Change of animal origin status, BSE/TSE risk
- Addition of manufacturing site – like for like equipment and processes
- Change in raw material grade – if down grading or removing requirement
- Change regarding shelf life – shortening current shelf life

Changes for which notification is given a minimum of 9 months prior to implementation:
- Change in formula, content, or make-up of a given standard liquid, powder or serum product.
- Significant manufacturing changes (equipment and process)
- Change of manufacturing environment (reduction in classification)
- Change of product storage conditions – if outside of currently validated range
- Change in product contact material of primary packaging that could impact product stability

Changes for which notification is given a minimum of 1 year prior to implementation:
- Addition of manufacturing site – not like for like
- Significant change to quality product release procedure

All customer specific supply, quality and/or change agreements for custom products that includes standard cell culture products supersede the above notification requirements. All change notifications for custom specific products will be delivered per the terms of the negotiated and approved agreements.
7.5 BioProcess Single-Use disposable products

Changes for which GE will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk. For variation of the changes below, the nature of the change and result of the risk assessment will guide change categorization and any notification timeframe (e.g. change in a wetted part form vs a non-wetted part form).

For custom products, notifications will be provided according to the following when changes are prompted by GE. For changes prompted by the customer, a formal notification will not be provided. Note that the ReadyToProcess column packed with chromatography resins are supported with change control notifications through product subscriptions to the ReadyToProcess column and the included chromatography resin. Notifications related to the column parts and packing will be according to the list below and notifications related to included chromatography resin will be according to 7.3 Bioprocess chromatography resins.

Changes for which notification is typically given 3 months prior to implementation (corresponding to BPOG level1):
- Change to the certificate and labelling, editorial changes
- Change in specification
- Change in shelf-life or storage - product improvement
- Change in packaging or packaging material
- Change to release testing procedures

Changes for which notification is typically given a minimum of 6 months prior to implementation (corresponding to BPOG level 2):
- Change regarding certificate (content) – product name, labelling, catalogue number
- Change of shelf-life or storage conditions
- Change to compliance/standards status
- Change of critical subcontractor
- Change in product/process contact material (wetted part) that results in alteration of the product quality, including form or fit – non-functional design changes (no raw materials changes)
- Change of manufacturing site location (that impacts product specification or form, fit and function)

Changes for which notification is typically given a minimum of 12 months prior to implementation (corresponding to BPOG level 3):
- Change to manufacturing equipment – significant changes (that impacts product specification or form, fit and function)
- Change to manufacturing process - significant changes (that impacts product specification or form, fit and function)
- Change to sterilization procedures - significant changes (e.g. gamma to moist heat, or change to validated range of operation)
- Change to product specification (design changes) for functional attributes
- Change in product/process contact material (wetted part) that results in alteration of the product quality – functional design changes or raw material
7.6 BioProcess instruments spare parts & accessories, and columns spare parts & accessories

Changes for which notification is typically given prior to implementation:

- Change of code numbers for spare parts

Changes for which notification is typically given a minimum of 6 months prior to implementation:

- Change in product/process contact material (wetted part) that results in:
  - Alteration of the product quality (form, fit and function)
  - Change to specification
  - Change to regulatory or compliance status

7.7 Software

No change is made to a launched version of a software. Changes/updates are introduced via new versions. Information letters for software and change description documents are published for each version of the software under the category change control notification. The information letter contains descriptions of different scenarios that can occur when the software is used. Actions to avoid or correct problems resulting from the described scenarios are suggested. The change description document describes the major implemented changes and improvements in the newest version of the software compared to older versions.
7.8 Cell and gene therapy Single-Use disposable products

Changes for which notification is typically given 3 months prior to implementation:
- Change to the certificate and labelling, editorial changes
- Change in specification
- Change in shelf-life or storage - product improvement
- Change in packaging or packaging material
- Change to release testing procedures

Changes for which notification is typically given a minimum of 6 months prior to implementation:
- Change regarding certificate (content) – product name, labelling, catalogue number
- Change to compliance/standards status
- Change of critical subcontractor
- Change in product/process contact material (wetted part) that results in alteration of the product quality, including form, fit or function (including raw material)
- Change of manufacturing site location (that impacts product specification or form, fit and function)
- Change to manufacturing equipment – significant changes (that impacts product specification or form, fit and function)
- Change to manufacturing process - significant changes (that impacts product specification or form, fit and function)
- Change to sterilization procedures - significant changes (e.g. gamma to moist heat, or change to validated range of operation)
- Change to product specification (design changes) for functional attributes

7.9 Cell and gene therapy instruments & accessories

Changes for which notification is typically given prior to implementation:
- Change of code numbers for spare parts

Changes for which notification is typically given a minimum of 3 months prior to implementation:
- Change in product/process contact material (wetted part) that results in alteration of the product quality (form, fit and function)
- Change to specification
- Change to regulatory or compliance status
7.10 Discontinuation Policy

Should GE decide to discontinue any bulk chromatography resin product, (including ReadyToProcess™ chromatography resins) customers registered for Change Control Notifications for that product shall be notified at least 3 years in advance.

For single-use disposable products the notification period for discontinuation will be minimum 1 year in advance.

For BioProcess instruments and columns, the Change Control Notification will be sent out when production of the instrument or column is discontinued. (For spare parts on instruments and columns installed by GE an End-of-Service notification will be sent to all customers 1 year before the service support period ends.)

Should GE decide to discontinue any standard cell culture product, customers registered for Change Control Notifications for that product shall be notified at least 1 year in advance.

For cell and gene therapy products the notification period for discontinuation will be minimum 1 year in advance.

However, there may be extraordinary situations due to external or internal factors where GE may have to inform of a discontinuation with shorter notice. GE reserves the right to inform with shorter notice than described in situations when non-standard events occur.

The “Policy for Discontinuation of BioProcess Chromatography media and single-use products” applies only to products for which subscription to change control notification is available on the web page www.gelifesciences.com/rsf.

8. Subscription to change notification

Products subject to change control notification are listed on www.gelifesciences.com/rsf. Registration at the Regulatory Support web page is required for notification. To receive change control notifications, customers need to register at this web site and subscribe to CCN. Each product for which notification is required must be selected.

8.1 Notification content

The notification contains the following information:

- identity of product (product name, article/code number)
- description of the change
- reason for change
- impact of change
- supporting data (when applicable)
- updated specification when applicable
- time line for the change
9. **Flow chart**

Flowchart for the change control procedure.

- Create change request
- Evaluation by Change team, including:
  - Risk assessment
  - Decision about Change Notification
  - Plan covering change evaluation and implementation activities
- Change control review board meeting
- Requested change approved?
  - Yes
  - Change control review board meeting
  - Requested change approved?
    - Yes
    - Change control review board minutes
    - Is notification required?
      - Yes
      - Generate Notification letter
      - Implementation of change
      - Change documentation
      - Archiving
      - Notification letter to customer
    - No
    - Implementation of change
  - No
  - Generate Notification letter
  - Implementation of change
  - Change documentation
  - Archiving

10. **Document Owner**

Customer Regulatory Support Leader
## 11. Revision History

<table>
<thead>
<tr>
<th>Revision Number</th>
<th>Section(s) Changed</th>
<th>Changes</th>
<th>Updated by</th>
</tr>
</thead>
</table>
| 04              | Section 3, Section 7.6, Section 7.7, Section 7.8-7.9, Section 7.10 | - Cell and gene therapy products are included  
- "Change to pressure holding part" is removed. It is already covered by "Change to regulatory or compliance status"  
- Text on software made general to include additional software  
- Cell and gene therapy products included in the standard  
- Editorial changes to the text | Ondina Åsberg |
| 03              | All | - Warehouse and distribution changes added  
- Significant manufacturing changes added to chromatography resins  
- Single-use products aligned with BPOG thoughts principle  
- Instruments and columns aligned with the change management part in ASME-BPE 2016  
- Cell culture media catalogue products included  
- Editorial changes to the text | Ondina Åsberg |
| 02              | - Entire document  
- Section 7  
- Section 7.2  
- Section 7.3  
- Section 8.1 | - Editorial change to the text  
- Clarifying sentence added: Time frames are based on the type of the change.  
- 7.2 Notification points have been clarified:  
  - primary packaging material  
  - editorial changes of analytical specification without implementation delay  
  - addition of new test method  
- 7.3:  
  - Xcellerex single-use products are added  
  - Change of manufacturing site have been moved to 6 months  
  - Notification points have been clarified  
  - Primary packaging material  
  - Vocabulary/nomenclature has been adjusted to clarify and better reflect the use of the terms in the Single-Use area, e.g.:  
  - Certificate of Quality  
  - Product release criteria  
  - Release testing procedures  
  - Sterilization procedure  
  - Product specification  
  - Part (form, fit and function)  
- 8.1 Notification content: Time line for the change have been added | Ondina Åsberg |
- The two documents have been merged to one, and the document has been moved to another document system and therefore has a new number.  
- No changes to "Standard for GEHC Life Sciences Change Control process for BioProcess columns and instruments" 70-5053-56 (last edition: AA). | Ondina Åsberg |
Changes to “Standard for GEHC Life Sciences Change Control process for designated products” 70-5032-65 (last edition: AE) are mainly:

- ReadyToProcess products and Wave products added
- Time for which notification is given prior to implementation is prolonged from 3 to 6 months and from 6 to 9 months
- Changes concerning shelf life, storage conditions and animal origin of raw material are added