



# Bioprocess security of supply – Whatman™ chromatography resins from GE

*A case study*

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Human medicine manufacturers need suppliers who will consistently deliver high-quality consumables over decades and communicate transparently when changes are required. GE Healthcare's approach with Whatman cellulose-based chromatography resins illustrates its commitment to security of supply for biomanufacturers. To address a critical raw material challenge, existing resin stock was reserved for these customers, and a suitable replacement was identified. Further investment was made to secure resin supply long term by transferring production to a modern facility. In both cases the resins were rigorously validated, and customers received frequent, detailed updates in addition to required change control notifications. Through a combination of cross-functional collaboration, a risk-based change management, and a controlled order intake process including tight collaboration with customers, shortages of human medicines and health products were avoided.

## Introduction

A consistent, high-quality end product is dependent on the use of equally consistent, high-quality key manufacturing components. Considering that a biopharmaceutical can have a lifetime of 30–50 years, a reliable, long-term supply of key manufacturing components is essential. Since the launch of Sephadex™ resin almost 60 years ago, GE has worked closely with industrial customers to support their success. One of many ways that GE continues to support key industrial customers over the long term is by developing and implementing a restrictive policy for discontinuation of BioProcess™ chromatography resins and single-use products. This policy states GE's commitment to continuing supplies of each of its BioProcess bulk chromatography resins, single-use products, and process-scale filtration products as long as any such products are knowingly used in an approved, registered process for the manufacturing of biopharmaceuticals. The full text is available at [gelifesciences.com/securityofsupply](http://gelifesciences.com/securityofsupply).

GE's Whatman cellulose-based chromatography resins became part of the BioProcess chromatography resin portfolio in 2008 as the result of an acquisition. After a

product life cycle review, GE's initial intention was to phase-out the whole product range. However, upon learning that several Whatman resins were used to manufacture human biopharmaceuticals, the company adhered to its discontinuation policy and re-committed to continue supplying these BioProcess chromatography resins.

In addition to stopping the intended phase-out, GE further demonstrated, through reactive and proactive measures, its commitment to secure supply of these resins to customers manufacturing human health products. To summarize, GE responded rapidly to an interruption in supply of a critical raw material, which ensured continued supply of cellulose-based chromatography resins to human health customers. The company also transferred manufacturing to a more modern manufacturing facility as part of the BioProcess resin security of supply program, which will further secure the supply of these resins over the long term. In this case study we describe a detailed approach for securing the supply of two cellulose-based resins. These are DE52, which has anion exchange properties and CM52, a cation exchanger.

## Rapid response to a raw material supply challenge

### Background

Cotton linter is a critical raw material for the manufacture of GE's Whatman cellulose-based chromatography resins. After the supplier of cotton linter notified GE that its manufacturing site was closing, a cross-functional team of GE staff initiated a search for a cotton linter material with the same performance as the existing material (referred to as "pre-change" cotton linter hereafter) in 2013. Additional requirements were that the supplier and its manufacturing site needed to be qualified in accordance with GE Healthcare Life Sciences' Quality Management System.

### Challenges and keys to success – raw material change

Finding a supplier of cotton linter that had similar technical properties as the raw material used to manufacture the Whatman brand resins was not simple. Samples from several different suppliers were received, as well as samples from a different manufacturing site of the original supplier. These samples were evaluated in small scale and in technical trials to find a replacement cotton linter that met the specifications. Because technical trials and validation runs had to be scheduled on top of the regular manufacturing, manufacturing output needed to increase significantly.

Keys to success for the raw material change project were:

- Engagement of a **cross-functional project team** with representatives from manufacturing, QC, QA, sourcing, R&D, customer regulatory support, and product management to handle the raw material change.
- Engagement of the **manufacturing team** to handle both the regular manufacture and the raw material change.
- Implementation of a **risk-based approach** to handle the raw material change, requiring the input and expertise of the cross-functional team.
- Effective **project management** focused on timelines, with a regular internal operating rhythm in the cross-functional project and monthly external communication updates to customers.

### Raw material validation

Cotton linter from another manufacturing site of the original supplier was identified as possibly the most suitable replacement. A comparability study was therefore performed to evaluate products manufactured with cotton linter raw material from the new manufacturing site (referred to as "post-change" cotton linter hereafter).

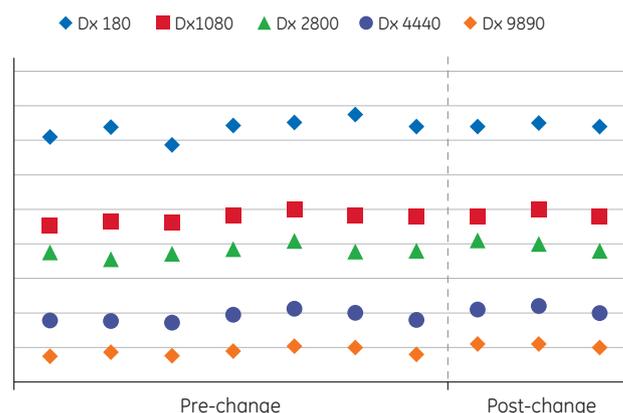
Practical handling and visual inspection of raw material, intermediates, and final products were evaluated by the unit that manufactured GE's cellulose-based chromatography resins. The following stepwise validation strategy was developed and executed.

#### 1. Raw material – comparability of the cotton raw material

Several lots of pre- and post-change cotton linter were evaluated by quality control analysis and comparison of certificate of analysis data. The post-change cotton linter was determined to be comparable to pre-change cotton linter and fulfilled the same physical and chemical acceptance criteria.

#### 2. Intermediate products – comparability of intermediates based on pre- and post-change cotton linter

Intermediates used in the manufacture of cellulose-based chromatography resins were evaluated by quality control analysis. Results showed that intermediates based on pre- and post-change cotton linter were comparable and fulfilled the criteria in the specifications. As a result of risk assessment of the change, testing of additional parameters (called verification) was performed to minimize risks that were identified with the change. In addition to the specification testing, intermediates were, for example, evaluated by iSEC (inverse Size Exclusion Chromatography) testing to ensure unchanged accessible pore volume and thus obtain similar chromatographic protein separation behavior. Five standardized dextrans with varying size were applied to the intermediate. The retention volume for each dextran was noted, and it was used to calculate distribution coefficients describing the fraction of available pores for a given dextran size. The addition of the verification analyses on top of standard QC analyses meant that methods needed to be developed by R&D and that baseline experiments needed to be performed on pre-change material, as well as on the technical batches and validation batches of the post-change material. Acceptance limits for the verification of the accessible pore volume were set to the mean of the references  $\pm 3$  standard deviations. The results showed that porosity for intermediates based on pre- and post-change cotton linter were within set acceptance limits and thus comparable (see Fig 1).



**Fig 1.** Accessible pore volume fraction for dextrans with varying lengths, measured by iSEC for intermediate based on pre- and post-change cotton linter material. Dx = dextran, the numbers correspond to different standardized dextrans.

### 3. Final product

Process qualification of the final products DE52 and CM52 was performed. Tests included in the current analytical specifications were done on three batches of each product. All tested batches were approved within set qualification limits. The results for one product, DE52, are presented in Table 1.

Two additional evaluations were performed on both DE52 and CM52. Fiber size dimension was tested by image analysis, and accessible pore volume was evaluated by iSEC testing. Results showed that fiber size dimensions and porosity were comparable for products based on pre- and post-change cotton linter.

Practical handling and visual inspection of raw material, intermediates, and final products were evaluated by the manufacturing unit and showed no major deviation compared to pre-change cotton linter.

## Proactive measures to secure long-term resin supply

### Background

As part of GE's BioProcess resin security of supply program, a decision was proactively made in 2013 to transfer production of Whatman chromatography media from Maidstone, UK to a modern global supply chain facility in Lindesnes, Norway. Like the UK facility, the Norwegian facility is also ISO-9001:2008 certified. With the internal transfer, more automation and some Environmental, Health, and Safety (EHS) improvements were obtained. For example, online process control of temperature during reaction and a completely closed system for handling of raw materials were installed.

## Challenges and keys to success – manufacture transfer

The manufacture transfer project from the UK to Norway was accompanied by a transfer of the design ownership from the UK manufacturing site to R&D for chromatography resins in Uppsala, Sweden. The transfer project involved, in effect, three GE sites in three European countries.

One of the challenges encountered while transferring manufacturing processes developed over 50 years ago was that not all development information from the pre-electronic era was accessible anymore. Much focus was therefore placed on transferring intangible knowledge from UK staff (e.g., manufacturing operators, QC operators, development engineers, planners) to staff at the Norwegian and Swedish sites. Employees from the “receiving” sites were present during normal manufacturing in UK. In addition, UK operators from the “transferring” site were present when manufacturing of technical batches started in the Norwegian facility.

Critical-to-quality (CTQ) properties of chromatography resins manufactured using complex biomolecules such as cellulose are described by the analytical specifications. However, consistent resin properties are also determined by the manufacturing process itself. At the same time, increased EHS requirements at a modern facility meant that the manufacturing process at the new facility was not an exact copy of the old one. Because of the risk-based approach that GE implemented to handle the manufacture change, verification testing of additional parameters with relevance to actual customer use was included in the comparability study.

**Table 1.** Process qualification results for DE52

	Analysis	Specification limits	Lot no. 1	Lot no. 2	Lot no. 3
1	Moisture (%)	70–76	73	74	73
2	Water regain free base (g/g of dry weight)	2.40–2.95	2.55	2.53	2.49
3	Water regain hydrochloric (g/g of dry weight)	2.70–3.50	2.93	2.93	2.81
4	Small ion capacity (meq/g of dry weight)	0.88–1.08	0.98	0.89	1.00
5	Protein Capacity (BSA) (0.01 M phosphate buffer pH 8.5) (g/g of dry weight)	0.55–0.85	0.59	0.61	0.58
6	Flow rate at 50 cm/H <sub>2</sub> O/cm column pressure (mL/cm <sup>2</sup> /h)	> 130	165	221	211
7	Flow rate at 75 cm/H <sub>2</sub> O/cm column pressure (mL/cm <sup>2</sup> /h)	> 180	231	305	297

During 2014 it became apparent that critical process steps in the Norwegian manufacturing facility needed to be optimized to ensure that the manufactured chromatography resins would fulfill the specifications and also perform satisfactorily in the additional verification tests. Validated DE52 material was released to customers in September 2015, and validated CM52 products were released in June 2016. Despite the delay in release of validated material according to the original project plan, security of supply to biopharmaceutical manufacturers was not at risk. By maximizing UK output and building stock (also an identified risk mitigation action), all registered biomanufacturers received sufficient UK-manufactured resin to support their manufacturing processes in 2014, 2015 and 2016, and shortages of human medicines and health products were avoided.

Keys to success for the manufacture transfer project were:

- Engagement of a **cross-functional project team** with representatives from both manufacturing sites, including QC, QA, sourcing, R&D, customer regulatory support, and product management, to handle the manufacture change.
- Engagement of the **manufacturing teams in UK and Norway** to handle both the regular manufacture and the manufacture change.
- Implementation of a **risk-based approach** to handle the manufacture transfer change, requiring the input and expertise of the cross-functional team.
- Effective **project management** focused on timelines, with a regular internal operating rhythm in the cross-functional project, monthly follow-up with an internal GE steering committee, and monthly external communication updates to customers.



Fig 2. DE52 flow rate at 50 cm H<sub>2</sub>O/cm.

## Manufacture transfer validation

A similar stepwise validation strategy was used for DE52 and CM52 as described for the raw material supplier project.

### 1. Intermediates – process qualification

Three batches of each intermediate were included in the process qualification to show comparability at the intermediate level.

### 2. Final product – process qualification

Process qualification was performed on three batches of each final product and compared with the historical outcome from the UK site.

### 3. Intermediates and final product – additional verification testing

Additional verification testing was done to show comparability.

Acceptance limits for the process qualification were the same as the specification limits. For additional verification testing on intermediates and final products, conclusions regarding comparability were based on testing of a limited number of reference batches produced in UK.

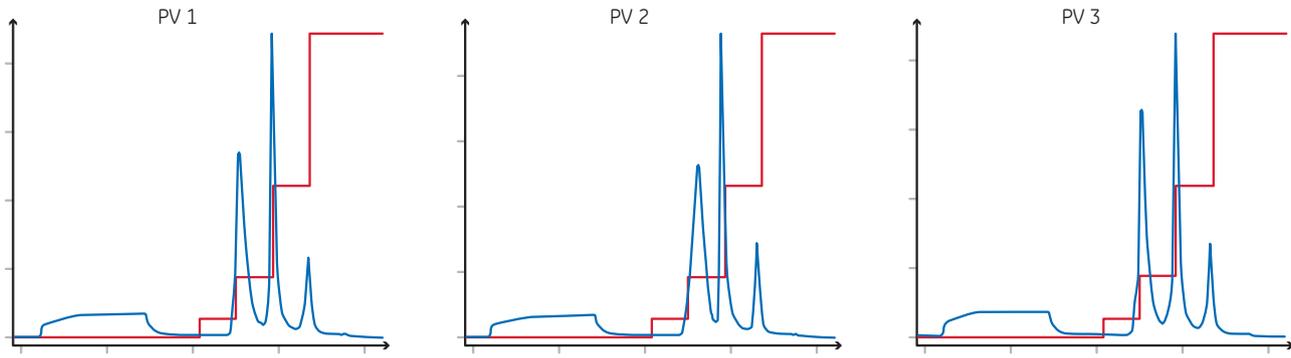
Examples of some results from the DE52 validation and verification are provided in Figures 2 and 3. Flow rate (Fig 2) is a CTQ parameter that is included in the product specification. Figure 3 shows results from one of the additional verification tests, plasma protein separation, which was chosen to mimic a customer application. Both the reference and validation batches separated the plasma proteins in three distinct peaks (see Fig 3). Slight variations in proportions between peaks could be observed between validation batches and also between reference batches. This can be explained by variations in the plasma sample and column packing. Comparable results were shown for validation and reference batches.

## Successful validation of DE52 and CM52 in Norway

With the internal transfer, a new modern facility at the Lindesnes site in Norway was introduced with comparable manufacturing equipment, manufacturing methods, test methods, and analytical specifications.

Based on a thorough internal technical transfer program, results from comparability studies, and process validation, it was concluded that DE52 and CM52 products manufactured in Norway can replace products manufactured in the UK. Furthermore, they can be supplied under the same product codes, which minimizes the change control burden for GE customers.

## Validation batches



## References

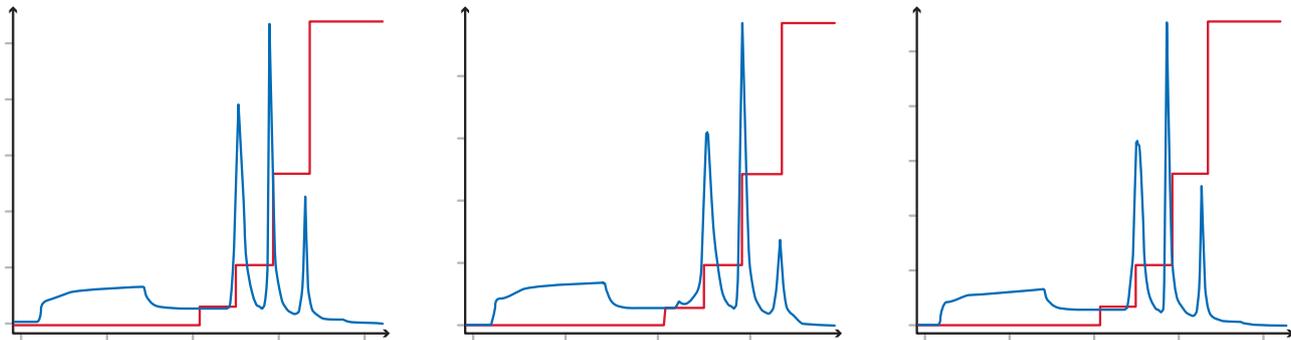
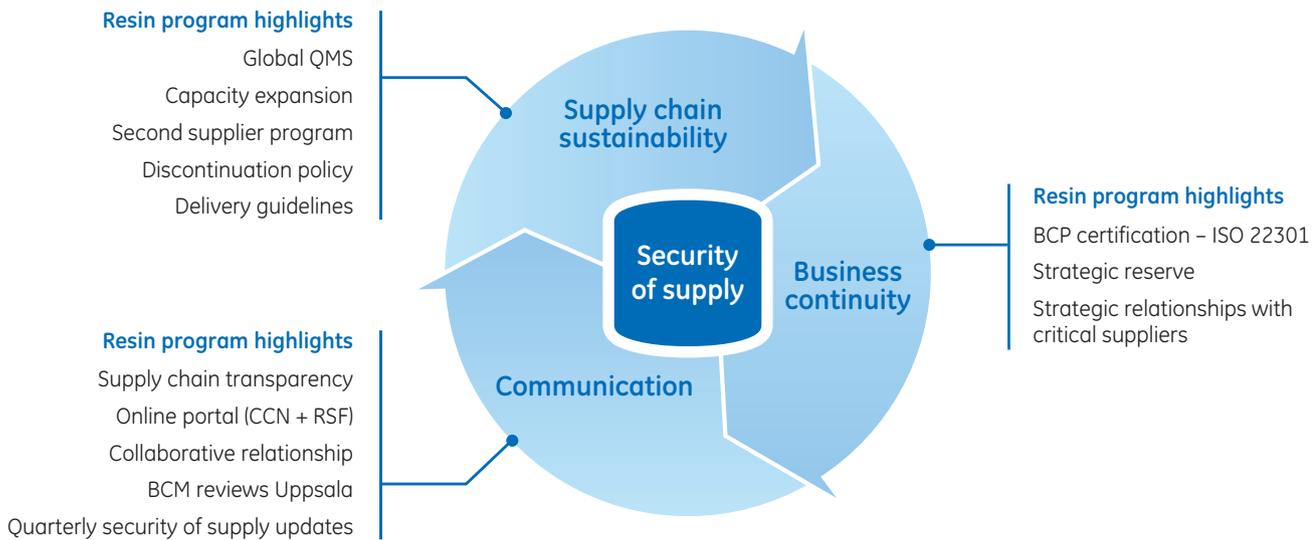


Fig 3. Plasma protein separation with process validation (PV) from Norway and reference batches from UK.

## Collaborative communication throughout both projects

In response to a challenge with supply of cotton linter raw material, a “controlled order intake process” for the sales of Whatman resins was implemented in 2013 to control use of the existing inventory and enable direct customer communication. On a yearly basis, the human health customer demand was established and compared to historical usage to ensure that all manufacturing processes of biopharmaceuticals could be supported. Sales were temporarily stopped for other customers. For example, because validation of Norwegian DE52 was delayed from 2014 to 2015, all human health customers needed to be supplied with UK products for an additional period to enable customer validation of the chromatography resins manufactured in Norway. The controlled order intake process was critical to ensure a continued supply to customers producing human medicines, diagnostics, and other products related to human health.

In 2013, historical customers from the previous three years were notified by letter of the implementation of the control order intake process. A Web site dedicated to the Whatman chromatography resins was published in early 2013 and was updated whenever new information became available. From the first half of 2013, during the process of validating the new raw material source followed by the manufacture transfer to Norway, affected BioProcess customers were provided with detailed monthly updates on the project status by e-mail until the last change control notification (CCN) was sent out in mid-2016. These monthly updates ensured that customers were informed in a timely manner of progress and changes in the project. In addition, customer visits and teleconferences with customers were crucial for transparency and ensured achievement of the project goal: all customers registered as manufacturing human health products received continued supply of resins while the projects were ongoing and until the controlled order intake process was removed. In other words, patients were never at risk of suffering from a shortage of their medicines resulting from an interrupted supply of these GE chromatography resins used in their manufacture.



**Fig 4.** GE's security of supply (SoS) framework for chromatography resins. The three elements that encompass GE's overall SoS approach – supply chain sustainability, business continuity, and communication – are shown here, along with program highlights specific for chromatography resins. Within the chromatography resin business, specific focus is currently placed within the second supplier program to identify and implement second suppliers of critical raw materials where possible (e.g., for the raw materials agarose and dextran), to have strategic relationships and long-term contracts with critical suppliers, and to expand manufacturing capacity to secure supply to customers. BCP = business continuity planning, BCM = business continuity management, CCN = change control notification, QMS = quality management system, RSF = regulatory support file.

Suppliers to the biopharmaceutical industry are required to have a process for change control. GE Healthcare Life Sciences' change control standard describes the risk management of change and how customers are informed about changes related to BioProcess chromatography resins and other key materials. Whatman resin customers who had signed up for GE's change control notification service (see [gelifesciences.com/rsf](http://gelifesciences.com/rsf)) received the CCNs for both the raw material supplier change and the manufacture transfer change to facilitate their own internal change control handling. In both projects, free samples of the validation batches were available to customers, in case they wanted to perform lab-scale verifications with post-change resin. Additional information on the validations and verifications was provided to customers who requested more support to their risk analyses of the changes.

## Conclusion

The case study described here shows the importance of many different aspects of GE's security of supply program (Fig 4) that were crucial to securing the supply of two Whatman chromatography resins (DE52 and CM52) used to manufacture human biopharmaceuticals:

- The importance of GE's discontinuation policy, without which these resins would have been phased out.
- GE's dedication to supply chain sustainability, by engaging a cross-functional team to find and validate a new supply of a critical raw material used in resin manufacture.
- GE's commitment to business continuity by transferring production to a modern facility.
- Customer communication and transparency with:
  - CCNs to registered customers.
  - Monthly status updates by e-mail to known human health customers.
  - Web information available to all.



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