

# Security of supply for chromatography media



# Manufacturing continuity in an uncertain environment

Manufacturing of biopharmaceuticals is a large commitment to the public health and helps save the lives of millions of people. The complex nature of biopharmaceuticals makes manufacturing a challenge, in which a consistent, high-quality end product is dependent of the use of equally consistent, high-quality key manufacturing components.

Key manufacturing components are often single-sourced. As it many times is costly and time-consuming to replace components of a regulated manufacturing process, it is important to secure the supply of these components. Considering that a biopharmaceutical can have a lifetime of 30 years or more, reliable, long-term supply of key manufacturing components is essential.

Chromatography medium (resin) is an example of a key manufacturing component. Being one of the world's leading suppliers of chromatography media, GE Healthcare Life Sciences has taken extensive preventive actions to help secure a continuous supply of media to our customers. We have implemented a security of supply program to help our customers maintain manufacturing of vital biopharmaceuticals, even under unforeseen circumstances.

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## Ever new challenges

For the last decades, higher productivity, purity, and yield have been the driving forces when designing manufacturing processes for biopharmaceuticals. Recent years' technical developments, leading to increased titers from upstream production steps, have also put increased demand on the capacity of downstream product purification steps. Technical performance properties such as binding capacity, selectivity, and productivity will continue to be of vital importance when designing purification processes. However, the choices you make today will impact your daily manufacturing process for several years ahead. Chromatography media are important components of the purification process, and in many cases it can be difficult to substitute media used in regulated manufacturing environments. Hence, parameters such as security of supply, reliable delivery lead times, and lot-to-lot consistency of your medium have become equally important as technical performance, and put high pressure on your supplier.

In view of today's complex global supply chains and recent years' financial turmoil and natural disasters, such as the volcanic eruption on Iceland in 2010, the earthquake and tsunami in Japan in 2011 (Fig 1), and hurricane Sandy that hit the US east coast in 2012, we are reminded of how vulnerable today's supply chains can be to unforeseen events. As the end products are intended for the treatment of millions of patients with serious and life-threatening diseases, actions to avoid disruptions in the supply chain need to be in place for the manufacturing of biopharmaceuticals.

## An experienced supplier for the biopharmaceutical industry

GE Healthcare is a 17 billion USD unit of the General Electric Company (NYSE:GE), employing more than 46 000 people worldwide. The company provides technologies for biomedical research as well as for biopharmaceutical development and manufacturing.

GE Healthcare Life Sciences, a division of GE Healthcare with more than 50 years of experience in the biotech industry, offers a wide range of technologies, products, services, and knowledge. Starting with the development of Sephadex™ in 1959, we have continued to provide innovative solutions to enable manufacturing of next-generation biopharmaceuticals. Over the years, GE Healthcare has supplied millions of liters of chromatography media, tens of thousands of process-scale columns, and thousands of chromatography systems. This track record of continued supply to the biopharmaceutical industry shows our commitment and capability. Today, our chromatography media are used in the majority of all manufacturing processes for FDA-approved biopharmaceuticals. Being a key solution provider for the biopharmaceutical manufacturing industry, we have implemented an extensive security of supply program for chromatography media to help secure business continuity for our customers, even under challenging conditions.



**Fig 1.** Earthquake and tsunami in Japan in 2011. Photo courtesy of AFP PHOTO/JIJI PRESS/TT.

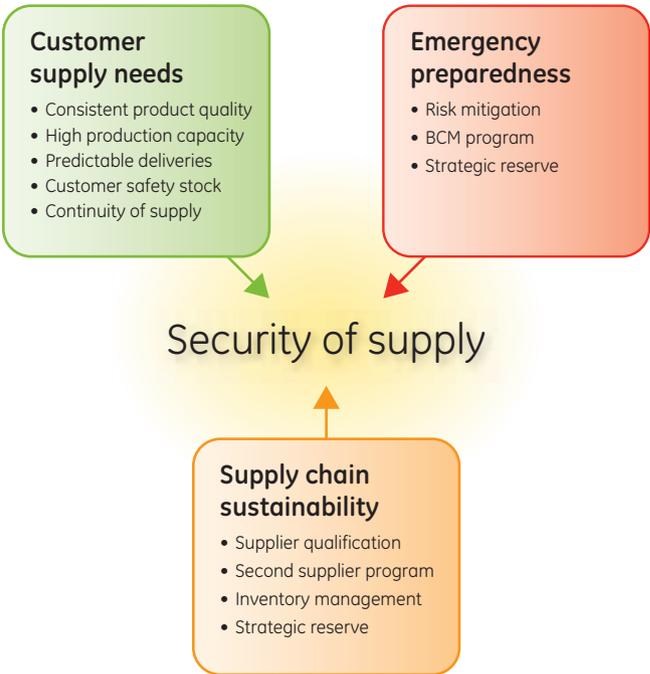
### Security of supply for chromatography media

Because of the unique properties of each chromatography medium and the complexity and costs associated with keeping several parallel manufacturing processes, chromatography media are often sourced from one, single supplier.

To meet the customer demand for security of supply for chromatography media, GE Healthcare has implemented a three-part program (Fig 2):

1. Consistent product quality and high manufacturing capacity to meet customer requirements and demands for fast and predictable deliveries, both short- and long-term.
2. Emergency preparedness to minimize the probability and potential impact of a serious incident at our manufacturing site. Our emergency preparedness includes an extensive business continuity management (BCM) program comprising a business continuity plan (BCP) following industry standards and a strategic reserve to enable deliveries of media for use in the manufacturing of human pharmaceuticals during business recovery.
3. Supply chain sustainability work comprising rigid standards for supplier qualification and management as well as a second supplier program and inventory management to minimize the risk of shortage of supply of critical raw materials for our production of chromatography media.

GE Healthcare also actively monitors and acts upon regulatory requirements for chemical compounds, to enable business sustainability and continuous supply to our customers.



**Fig 2.** GE Healthcare's security of supply program for chromatography media.

## **High manufacturing capacity with consistent product quality**

GE Healthcare has one of the world's largest manufacturing capacities of chromatography media. At our 160 000 m<sup>2</sup> manufacturing site in Uppsala, Sweden, over 1400 different media are manufactured (Fig 3). The manufacturing site is certified according to ISO 9001:2008 and consists of two physically separated multipurpose manufacturing facilities.



**Fig 3.** Manufacturing of chromatography media at the Uppsala site.

### **Capacity**

GE Healthcare produces over 300 000 L chromatography media annually. We continuously expand our manufacturing capacity. Recently we invested more than 100 million USD in production upgrades to meet the growing demand for our products. Manufacturing upgrades include investments to cut bottlenecks and decrease cycling times, but also manufacturing scale-ups. As an example, our manufacturing batch sizes of MabSelect SuRe™ protein A media have increased three-fold over the last years. Our scale of production allows us to quickly adjust to increasing customer needs.

### **Quality**

To enable delivery of products with sustained quality, our manufacturing methods are validated for high lot-to-lot consistency. Monitoring of variations in raw material and a stringent process control allow us to level out variations in the final products.

Regular customer audits of our manufacturing site act as catalysts for continuous improvements of our product quality and production processes.

In accordance with our change control standard for supporting customers in their risk assessments, GE Healthcare informs subscribers of change control notifications about required changes associated with the manufacturing of our BioProcess™ chromatography media.

GE Healthcare was one of the pioneers in providing regulatory support files (RSFs) to support customers with detailed information on performance, stability, extractable compounds, and analytical methods for process chromatography media. The information included in these files is a valuable starting point for process development and

validation, for preparation of standard operating procedures and quality control, and as support for clinical and marketing applications to regulatory agencies. RSFs can help reduce development costs and time to regulatory filing.

### **Continuity of supply**

Long-term supply of chromatography media is equally important as short-term supply. We are determined to continue the supply of each of our BioProcess chromatography media as long as such products are knowingly used in approved, registered manufacturing processes for human therapeutics. This provision is formalized in a discontinuation policy signed by the CEO of GE Healthcare Life Sciences.

### **Safety-stock offering**

GE Healthcare offers its customers the possibility of carrying a safety stock. The safety stock is a customer-dedicated inventory, held by GE Healthcare to a monthly fee to minimize downtime or product loss caused by incidents at our customer's site during a manufacturing campaign or regular production. The customer safety-stock offering is a flexible solution, where the customer chooses product, volume, retention time, and location of the stock to any of our global facilities. The customer safety stock comes with or without purchase obligation of the stocked products.

### **Emergency preparedness at GE Healthcare's manufacturing site for chromatography media**

GE Healthcare has manufactured chromatography media in Uppsala, Sweden since the late 1950s without any major incidents. The manufacturing site is located in a politically and geographically stable area that is not considered to be at risk of natural disasters.

Safety is of highest priority at our manufacturing site and we have performed extensive activities to minimize risk for incidents. In 2011, the Uppsala manufacturing site was awarded with the Global Star™ certificate within the GE Group. The Global Star award is given to sites that meet the GE health and safety standard, which is equivalent to the occupational safety and health administration (OSHA) standard in the USA. The reward shows that the Uppsala site is managed and run with minimal risk for customers, employees, and the environment, and was renewed in 2013.

To safeguard production also for the future, a business continuity management (BCM) program was implemented at the manufacturing site in 2003 (Fig 4). The program identifies and evaluates risks to critical assets, and mitigates the effects of unforeseen losses by having in place continuity and recovery strategies, developed at both corporate and business levels.

Should an incident occur, dedicated organizations, including emergency response team (ERT) and crisis management team (CMT), have been set up at the site in Uppsala to mitigate and minimize the impact for our customers. The teams have mandatory training on a yearly basis.

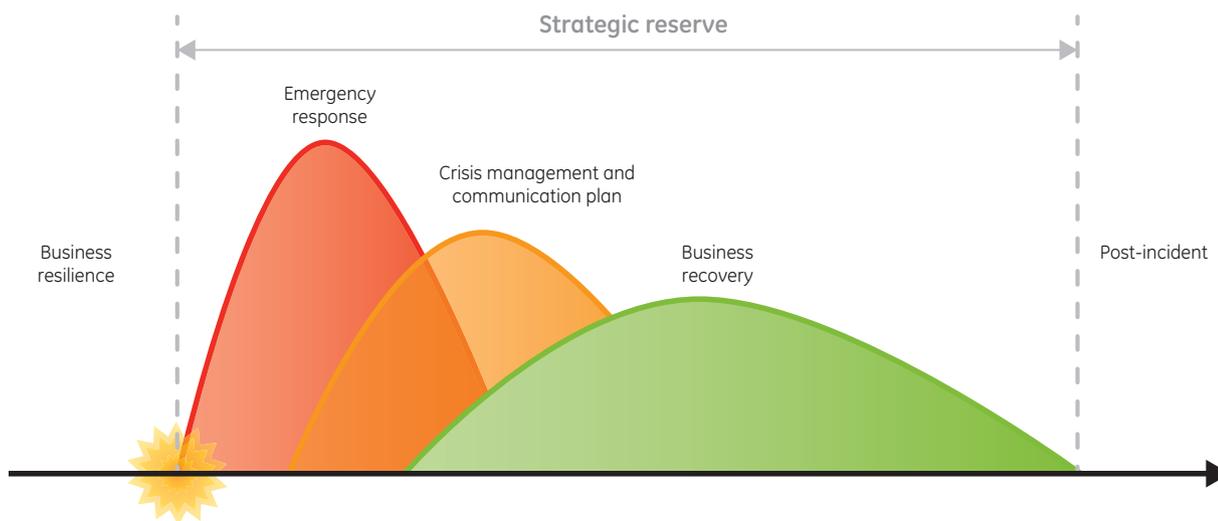


Fig 4. GE Healthcare's BCM program to enable continuous operations in case of a major incident. Estimated recovery time is six months

The BCM framework is based upon the British standard BS25999-1 and has been audited by external organizations. Our plan is to obtain the recently released ISO 22301 certificate for business continuity management for the Uppsala manufacturing site within the next few years.

If an unforeseen incident occurs, the response activities will be structured in three phases:

1. Emergency response phase: secure and protect the health and safety of all employees, and protect and save company assets and the environment.
2. Crisis management phase: impact management, including communication with customers.
3. Business recovery phase: restore lost capacity and serve our customers' needs by interim solutions such as the strategic reserve (see "The strategic reserve") of chromatography media.

As an integrated part of the BCM program, regular business impact analyses and risk assessments are performed both internally and by third parties. The assessments have concluded that the main risk identified is considered to be a fire or explosion caused by the large amounts of organic solvents used on the site. Based on the risk assessments and associated disaster simulations, extensive risk mitigation activities and business recovery strategies have been implemented. One example of a preventive action is the design of the manufacturing buildings with multiple fire cells. In case of a fire, the cells can withstand heat for up to 60 minutes even if the sprinkler system goes down. This precaution limits the damage of fires or explosions and helps prevent major disasters from occurring.

Other preventive actions to minimize the probability of serious incidents are the establishment of underground solvent-storage tanks and drainage basins to minimize the risk of explosions and fires in the tank yard and the introduction of nitrogen blanketing within our bioreactors to prevent hydrogen ignition.

An important part of the recovery plan is the possibility, if required, to move manufacturing lines within or in between our two independent on-site manufacturing facilities. In such a scenario, a recovery time of up to six months has been estimated until affected processes are validated and manufacturing is up and running. During the recovery time, our strategic reserve of chromatography media will cover for potential supply interruptions in deliveries for approved and registered biopharmaceutical manufacturing processes. For certain products, recovery time can be up to 12 months and this is subsequently reflected in the strategic reserve volume.

### The strategic reserve

In case of an incident that severely affects GE Healthcare's manufacturing of chromatography media, a strategic reserve of media has been established to cover for deliveries during the business recovery phase (Fig 5). The reserve comprises media that, to the best of GE Healthcare's knowledge, are used in approved and registered manufacturing processes of human therapeutics. This back-up inventory covers an approximate 6 to 12 months' supply, depending on the recovery plan for each product, until manufacturing is up and running according to our business continuity plan.



Fig 5. Strategic reserve comprises chromatography media used in approved and registered manufacturing processes of human therapeutics.

The reserve is located in inventories outside the manufacturing site in Uppsala. Customized media and media with shelf life less than two years are excluded by default from the strategic reserve because of shelf-life restrictions. Currently, over 70 000 L of chromatography media, representing more than 60 types of media, is stored in the reserve. The products and volumes kept in the reserve are reviewed annually.

To maximize shelf life of the included media, the content is rotated on a regular basis.

It is important to note that the content of the reserve will only be used in the case of a major incident, at our production site in Uppsala or at the site of any of our suppliers of critical raw materials, which severely affects our manufacturing of media. Usage of the content outside its purpose would erode the reserve and limit GE Healthcare's ability to serve customers in case of an emergency. The reserve is not earmarked for any specific customer and cannot be used as a safety stock if something happens at our customer's manufacturing site.

In case of utilization of the strategic reserve, a controlled order intake process will be implemented. Withdrawals from the strategic reserve will be prioritized case by case based on urgency. The prioritization will favor the immediate use of the medium in a manufacturing process for an approved pharmaceutical for human use, to enable the supply of the pharmaceutical to the public.

### **Supply chain sustainability**

With today's complex supply chains, regulatory authorities put pressure on pharmaceutical manufacturers to have control over their full supply chains. Emphasis is put on the importance of having a structured and risk-based process of choosing and evaluating suppliers for the pharmaceutical production.

At GE Healthcare, we require that all our suppliers have in place a quality management system, corresponding to ISO 9000 or equivalent. Our suppliers are audited (physical or desk) on a regular basis by trained and qualified supplier quality engineers according to a strict quality management system. Among the requirements on our suppliers are:

- Supplier integrity statement: compliance with GE Healthcare's high ethical and regulatory standards
- Supplier quality agreement: change control notifications, clean room standards, and document retention
- Supplier selection checklist: detailed information on quality systems, financial status, compounds subjected to regulations such as REACH, components of animal origin, and more
- Supplier BCP: risk identification and recovery strategies for critical raw materials

Risks associated with geographical location and potential impact on supply security is also assessed in the choice of supplier.

In response to the recent natural disaster in Japan 2011, GE Healthcare has initiated a supply chain sustainability program to further strengthen our supply chain security. The supply chain sustainability strategy comprises critical and important raw material\* for BioProcess chromatography media used in approved and registered manufacturing processes. Should a severe incident happen in our own supply chain, we can make use of our strategic reserve to cover for potential interruptions in the supply for registered manufacturing processes.

In addition, our supply chain sustainability program includes:

- Identification of at least one second supplier for most of our critical and important raw materials to reduce implementation time if required during an emergency
- Implementation of second suppliers for selected raw materials (prioritization based on financial and supply risk)
- Additional in-house inventory of selected raw materials

GE Healthcare has assessed the time for implementation of second suppliers for all critical and important raw materials. In cases where the estimated time for implementation of a second supplier will exceed the supply coverage period of the strategic reserve, we will either implement a second supplier proactively or build a dedicated raw material inventory.

Implementation of second suppliers is a continuous process that will be conducted for selected raw materials at a controlled rate to enable long term supply of chromatography media. GE Healthcare is aware of that changes to chromatography media used in registered manufacturing processes need to be assessed and verified by our customers.

During the last years, second suppliers have been implemented for the heparin ligand used in Heparin Sepharose™ products and for N,N-methylen bisacrylamid used in Sephacryl™ products. For the protein A ligands used in MabSelect™ and MabSelect SuRe media, multiple manufacturing sites have been implemented. Ongoing projects include implementation of a second supplier for agarose used as a backbone in our base matrices.

Figure 6 illustrates the emergency preparedness for interruptions in the supply chain of GE Healthcare BioProcess chromatography media used in approved and registered manufacturing processes. In the case of an incident that severely affects our supply chain, close to 100% (customized media and short shelf life products are excluded) of our chromatography media are covered by the strategic reserve. For raw materials, we have identified second suppliers for most of the critical and important raw materials used in our production of media, for fast implementation in case of an incident. In cases where we have not been able to identify a second supplier, we manage supply risk by commercial contracts and raw materials safety stocks.

\* GE Healthcare's definition of critical raw material in this context is a raw material with a complex chemical structure and that has a significant impact on the performance of the finalized product.

When introducing second suppliers of critical raw materials, GE Healthcare will perform thorough comparability studies and process validation to ensure interchangeability. Customers subscribing to our change control notifications will be notified well in advance of the implementation of a second supplier. During the change control notification period, typically nine months, the customer will have the opportunity to request samples for evaluation before the change is implemented in production. In addition, extended documentation packages, including more comprehensive data to support risk assessments, will be available upon request.

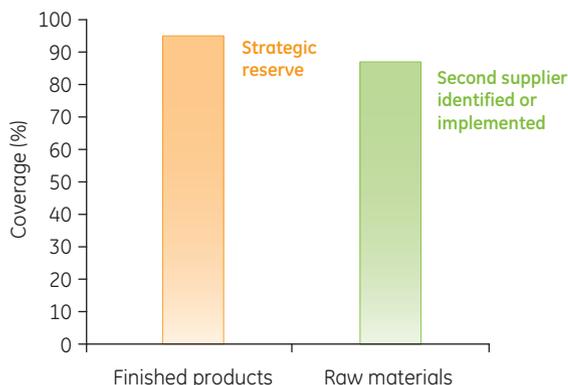
## Trust and support throughout the product lifecycle

Higher productivity, purity, and yield have been the driving forces when designing manufacturing processes for biopharmaceuticals. The choices you make today will impact your manufacturing process for several years ahead. For the development of an optimized process and for a consistent and cost-effective biopharmaceutical production, a close collaboration between the manufacturer and its supplier is beneficial (Fig 7).

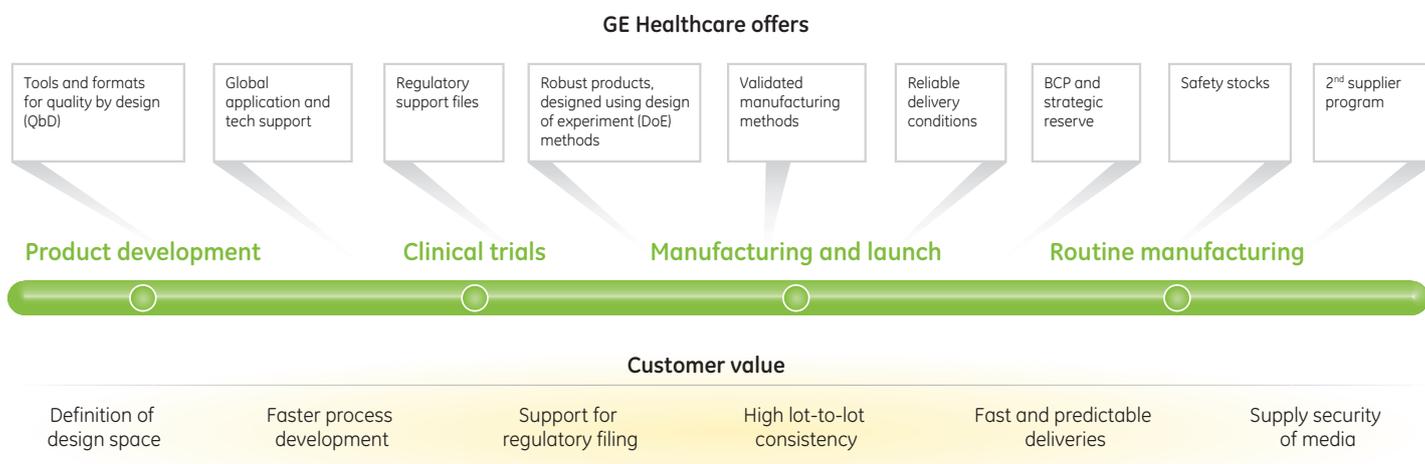
At GE Healthcare, we offer products, services, and support to assist you throughout your product's lifecycle.

For faster screening of purification conditions in early development phase, we provide tools that facilitate process development and significantly contribute to a shortening of the overall development time. When approaching clinical trials, registration with the authorities becomes necessary. To assist in this process, we provide regulatory support files (RSFs) for our media, including detailed information on performance, stability, extractable compounds, and analytical data. The RSFs are a good starting point for process development and validation.

To find out more about how we can be your trusted supplier, please contact your local sales representative.



**Fig 6.** Emergency preparedness for chromatography media used in approved and registered processes with respect to finished goods and critical and important raw materials. Left bar shows approximate percent of GE Healthcare's chromatography media covered by the strategic reserve. Right bar shows fraction of critical or important raw materials, used in production of chromatography media, for which second suppliers are identified or implemented.



**Fig 7.** A close collaboration between the manufacturer and its supplier generates customer value from biopharmaceutical development to manufacture.

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GE Healthcare UK Limited  
Amersham Place  
Little Chalfont  
Buckinghamshire, HP7 9NA  
UK

GE Healthcare Europe  
GmbH, Munzinger Strasse 5  
D-79111 Freiburg  
Germany

GE Healthcare Bio-Sciences Corp.  
800 Centennial Avenue, P.O. Box 1327  
Piscataway, NJ 08855-1327  
USA

GE Healthcare Japan Corporation  
Sanken Bldg., 3-25-1, Hyakunincho  
Shinjuku-ku, Tokyo 169-0073  
Japan

For local office contact information, visit  
**[www.gelifesciences.com/contact](http://www.gelifesciences.com/contact)**

[www.gelifesciences.com](http://www.gelifesciences.com)

GE Healthcare Bio-Sciences AB  
Björkgatan 30  
751 84 Uppsala  
Sweden



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