ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

Non-Confidential Report

Legal name of Applicant(s): *GE Healthcare Bio-Sciences AB*

Submitted by: *GE Healthcare Bio-Sciences AB*

Substance: *4-Nonylphenol, branched and linear, ethoxylated substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof*

EC No: -

CAS No: -

Use title: *Industrial use of emulsifiers containing nonylphenols ethoxylated for the manufacture of chromatography resins used by the biopharmaceutical industry, food & beverage sector and academia.*

Use number: *1*

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TABLES

FIGURES

LIST OF ABBREVIATIONS

AfA	Application for Authorisation
AoA	Analysis of Alternatives
API	Active Pharmaceutical Ingredient
BB	Big Beads
BEI	Biological Exposure Indices
CAGR	Compound Annual Growth Rate
CSR	Chemical Safety Report
ECHA	European Chemicals Agency
EEA	European Economic Area
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
EUR	Euros
FBE	Pre-treatment for emulsifiers (active carbon filter)
FBET	Pre-treatment for emulsifiers in toluene
FDA	U.S. Food and Drug Administration
GE	General Electric
GEHC	General Electric Healthcare
GEHC LS	General Electric Healthcare Life Sciences
GDP	Gross domestic product
Kg	Kilogram
NPE	Nonylphenol, ethoxylated
NPI	New Product Introduction
NPV	Net Present Value
NUS	Non-Use Scenario

NYSE	New York Stock Exchange
OECD	Organization for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic to reproduction
PPE	Personal Protective Equipment
R&D	Research and Development
SEA	Socio-Economic Analysis
SVHC	Substance of Very High Concern
USA	United States of America
UVCB	Substances of Unknown or Variable Composition
vPvB	Very Persistent, very Bioaccumulative
VU	Vrije Universiteit Amsterdam
WS	Work Stream
WTP	Willingness-To-Pay
WWTP	Wastewater Treatment Plant

DECLARATION

We, *GE Healthcare Bio-Sciences AB*, request that the information blanked out in the "public version" of the analysis of alternatives (AoA) and socio-economic analysis (SEA) is not disclosed. We hereby declare that, to the best of our knowledge as of today (May 20, 2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature:

Date, place:

May 15th 2019, Uppsala, Sweden

Cecilia Sjöstedt, Managing Director, GE Healthcare Bio-Sciences AB, Uppsala

SUMMARY

The Applicant, GE Healthcare (GEHC) Bio-Sciences AB, requests authorisation for continuing the use of emulsifiers containing 4-Nonylphenol, ethoxylated (NPE), in the manufacturing process of chromatography resins. GE Healthcare Bio-Sciences AB (the Applicant) is a division of GEHC LS. GEHC LS is part of GEHC and ultimately of the General Electric (GE) Company (NYSE: GE). GEHC LS provides expertise and tools for a wide range of biotechnology and life sciences applications, including basic research on cells and proteins, drug discovery research, as well as tools to support large-scale manufacturing of biopharmaceuticals.

NPE is used by the Applicant at its production site in Uppsala, Sweden, as a component of the emulsifiers used during the preparation of mainly agarose-based intermediate resins, which are further processed to produce approximately 120 chromatography resins. These resins are widely used in several industrial and research applications for the purification and analysis of complex biological mixtures. The chromatography resins constitute a main component in the downstream processing of many biopharmaceutical applications such as the production of different biological Active Pharmaceutical Ingredients (API's). In addition, NPE-dependent chromatography resins are also used in academic research, such as genetic engineering and drug discovery, and in the food & beverages industry analytics.

NPE -containing emulsifiers are critical substances for the manufacture of chromatography resins, and many of the characteristics of the end-product chromatography resins are linked to NPE's properties. During the production of intermediate resins, emulsifier containing NPE is added during the emulsification step to aid in the formation of aqueous droplets dispersed in a solvent phase. These droplets contain the solubilized material that form the physical matrix of the intermediate resins. Upon cooling, these droplets form - particles whose size, shape and physical properties determine the characteristics of the different chromatography end-products. In this sense, the emulsifier containing NPE fulfils the following key functionalities in this use: reduction of interfacial tension to facilitate the formation of agarose aqueous solution/solvent solution emulsion, facilitation of droplet size reduction to reach the targeted drop size distribution, droplet stabilization during cooling and agarose particle formation, and low interference with other process conditions and other processing aids.

The quantities and types of NPE-containing emulsifiers used in each process vary depending on the type of chromatography resin produced. Due to the sensitive nature of the applications in which chromatography resins are used, especially in the manufacture of human therapeutics, in which any changes to the manufacturing processes and processing aids must be thoroughly evaluated to secure that the human therapeutic characteristics are not altered, substitution can only be considered successful if no changes in the properties of the final chromatography resins are observed.

The Applicant started R&D efforts for substituting emulsifiers containing NPE in 2003. These efforts include several literature searches as well as the commissioning of an external research

institution for the identification of potentially suitable alternatives. An initial list of alternatives was created and further narrowed down, taking into account various criteria, such as previous experience with the identified substances, safety concerns, process compatibility and commercial availability of the alternatives, among others. Laboratory and pilot scale testing are still ongoing to address the technical feasibility of the prioritized alternatives. These alternatives are selected emulsifiers from the phosphate ester emulsifier groups.

Based on initial test results and the activities required for implementing an alternative in all products affected, the Applicant foresees a period of 12 years from the sunset date (review period) for achieving full substitution of emulsifiers containing NPE. This period comprises all further R&D activities, pilot- and full-scale testing, commercial scale-up, and customer notification for all affected chromatography resins. Due to economic and technical considerations, substitution of resin families must be carried out in a staggered manner, meaning that implementation of alternatives in each product family will follow a sequential order. The priority for substitution was set according to the quantity of NPE-containing emulsifiers used in the production of each family group.

Implementation of an alternative in the manufacturing process of chromatography resins is a challenging task. Many activities must be completed before successfully switching to an NPE-free process: development of characterization methods and a product base line, development of production base methods, installation of reactors and product verification, technical trials and process verification, process and design validation, and notification of changes to customers. All these tasks must be completed for each product group, and if failure occurs at some point during the implementation phase, these must be started again with another alternative. The process is thus expected to be iterative and expand over several years. The overall substitution timeline for this application is shown below.

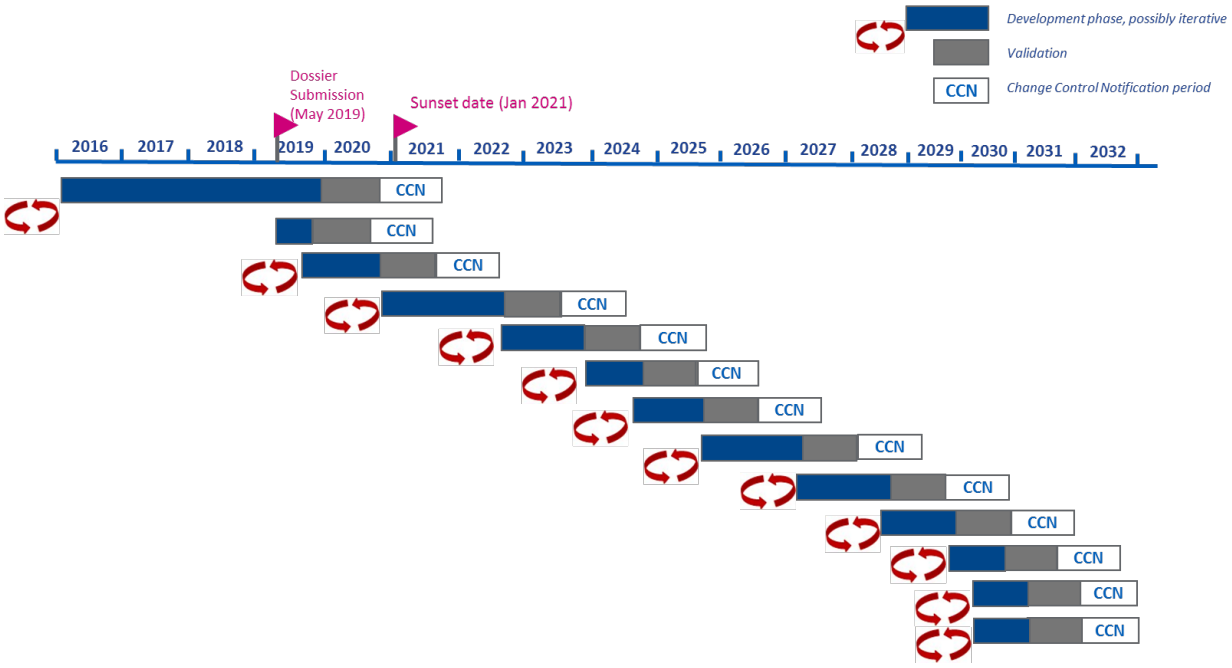


Figure 1: Estimated substitution timeline for chromatography resin families manufactured with emulsifiers containing NPE.

The main socio-economic benefit of continued use of NPE-containing emulsifiers is the continued supply of the affected chromatography resins to approximately 190 approved and registered manufacturing processes of biopharmaceuticals and consequently continued supply of medicines for treatment of millions of patients with serious, possibly life-threatening diseases. On top of this, a granted review period would include protection of profits for the Applicant, and continued employment of a highly skilled workforce at the Uppsala site,

The conclusions of the SEA show that the benefits of a granted authorisation by far outweigh the environmental impacts of the continued use of emulsifiers containing NPE, with socio-economic benefits ranging from [redacted] to [redacted] (lower and upper bounds, only for the Applicant and its employees) and a maximum of [redacted] of NPE emissions over a 12-year review period. A non-granted authorisation would lead to a socio-economic impact of more than [redacted] per kg of avoided NPE emission. It is important to note that socio-economic impacts per kg of avoided NPE emissions (over 12 years) are highly underestimated since reported socio-economic impacts of a non-granted authorisation are underestimated (only very minimum impacts have been reported and impacts to patients have not been monetised) while the emissions to the environment are certainly highly overestimated (the applicant foresees to have [redacted] NPE annual emissions as a very maximum only in the very worst-case scenario of failure in the process of substituting the use of NPE-containing emulsifiers). Current emissions are approximately [redacted] NPE per year.

Since the benefits associated with the continued used of emulsifiers containing NPE outweigh the risks to the environment, and since there are currently no suitable

alternatives to the emulsifiers containing NPE in this use, the Applicant believes that the request of a 12-year review period is justified.

1 AIMS AND SCOPE OF THE ANALYSIS

1.1 Aims

The following substance is subject to this Application for Authorisation (AfA):

Table 1: Substance covered by this AfA.

#	Substance	Intrinsic property(ies)[1]	Latest application date[2]	Sunset date[3]
43	**4-Nonylphenol, branched and linear, ethoxylated** Substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof EC No: - CAS No: -	Endocrine disrupting properties which cause probable serious effects to the environment	4 July 2019	4 January 2021

[1] Referred to in Article 57 of Regulation (EC) No. 1907/2006

[2] Date referred to in Article 58(1)(c)(ii) of Regulation (EC) No. 1907/2006

[3] Date referred to in Article 58(1)(c)(i) of Regulation (EC) No. 1907/2006

'4-Nonylphenol, branched and linear, ethoxylated' is categorized as a substance of very high concern (SVHC) and is listed on Annex XIV of Regulation (EC) No 1907/2006. The substances covered by the entry '4-Nonylphenol, branched and linear, ethoxylated substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof' (from here on addressed as "NPE") are identified as substances meeting the criteria of Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because (through their degradation) they are substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH. Adverse effects are evaluated in detail in a Chemical Safety Report (CSR). It is still unclear whether NPE should be categorized as a threshold or non-threshold substance, therefore the socio-economic analysis (SEA) route is followed.

The Applicant GEHC Bio-Sciences AB applies for authorisation to continue the use of emulsifiers containing NPE for the manufacture of chromatography resins on a single

production site in Uppsala, Sweden. A CSR prepared as part of this AfA is referenced here to provide context for the SEA part of this document.

The aim of this document is broken into two primary categories:

a) **The AoA**: to present a detailed description of the efforts and activities undertaken by GEHC Bio-Sciences AB to find suitable alternatives to emulsifiers containing NPE in the manufacture of chromatography resins. Potential alternative emulsifiers were evaluated for their technical and economic suitability. These alternatives were tested against various functional and process parameters to determine their suitability for replacing the emulsifiers containing NPE, starting with an initial longlist of alternatives and narrowing it down to a shortlist of a few candidates according to the pre- defined criteria.

b) **The SEA**: to demonstrate that the socio-economic benefits associated with the continued use of emulsifiers containing NPE by the Applicant outweigh the remaining risks to environment associated with prevalent use conditions.

1.2 Scope - uses

GEHC Bio-Sciences AB manufactures NPE-dependent chromatography resins at its facility in Uppsala, Sweden. The impact assessment, therefore, covers specifically the area where this facility is located - as part of the European Economic Area (EEA) - and takes into account the economic, social and environmental impacts resulting from a non-granted authorisation.

For the purpose of this SEA, an assessment period of 12 years was defined. Because the sunset date for NPE is in January 2021, the time period covered by the SEA runs from 2021 to 2032 (taking 2021 as a base year for calculations).

2 "APPLIED FOR USE" SCENARIO

2.1 The GE group and its Healthcare Life Sciences division

GE Healthcare Bio-Sciences AB (the Applicant) is a division of GEHC LS. GEHC LS is part of GE Healthcare (GEHC) and ultimately of the General Electric (GE) Company (NYSE: GE). Globally, GEHC has more than 47,000 employees in over 100 countries. It is present in all regions worldwide (Asia-Pacific, Europe, Middle East, Africa, USA-Canada and Latin America).

GEHC LS provides expertise and tools for a wide range of biotechnology and life sciences applications, including basic research on cells and proteins, drug discovery research, as well as tools to support large-scale manufacturing of biopharmaceuticals. It also supplies leading contrast agents, Positron Emission Tomography and nuclear medicine pharmaceuticals for diagnostic imaging for disease such as cancer, heart disease and neurological disorders.

GEHC LS employs more than 11,000 people in more than 100 countries with headquarters in Amersham, United Kingdom. The company has manufacturing and R&D capabilities in, Europe and Asia. GEHC LS is not a biopharmaceutical company and does not manufacture or sell biological APIs or medicines on the global market, but the products manufactured by GEHC LS are extensively used by biopharmaceutical companies to manufacture biological APIs formulated in medicines.

GEHC Bio-Sciences AB is the legal entity representing GEHC LS operations in Uppsala, Sweden, and is the focus of this application for authorisation. Figure 2 shows the business units of GEHC LS.

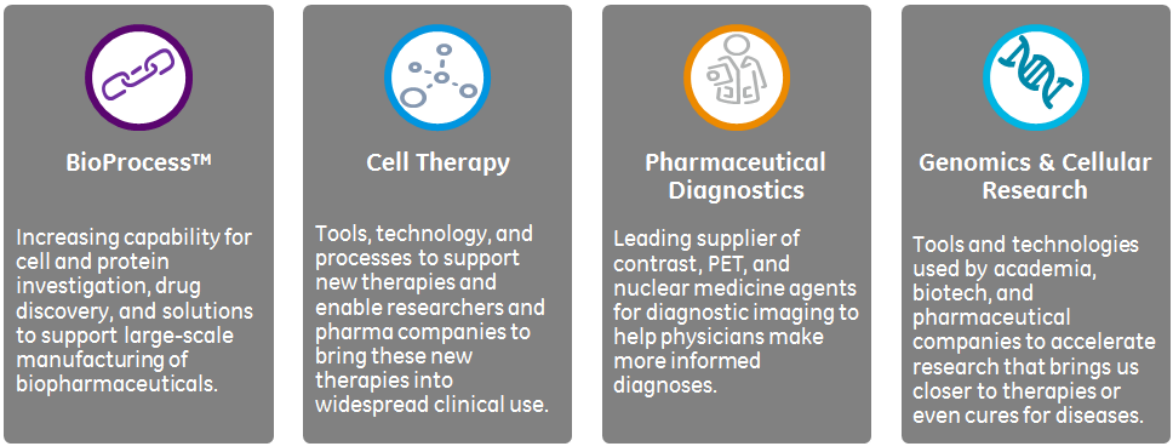


Figure 2: Business units GEHC LS.

2.2 Uppsala production site

GEHC LS's production facility in Uppsala is the sole manufacturing site within the EEA which produces NPE-dependent chromatography resins. The factory was acquired by GE from

Amersham in 2004 and has been developing chromatography resins for decades, with several Nobel laureates being connected to the technology.

Approximately 1,200 people (full time employees – FTE) are employed at GEHC LS's Uppsala facility. Out of those 1,200 workers, around [redacted] employees are directly involved in the manufacture of NPE-dependent chromatography resins. In 2017, GEHC LS's expenses with salaries of workers involved in the manufacture of NPE-dependent chromatography resins amounted to approximately [redacted].

GEHC Bio-Sciences AB is the largest private employer in Uppsala and its activities contribute to the growth of the Uppsala region and in particular to the biotechnology and life sciences sector. GEHC LS plans to invest up to USD 350 million until 2022 (up to EUR 300 million[1]) into the company's bioprocessing equipment and consumables site in Uppsala because of the strong demand from the biopharmaceutical sector for chromatography resins and equipment. Investments related to NPE-dependent chromatography resins that have not yet been fully depreciated amount to more than [redacted]. Total investment in the Uppsala site in the past 10 years (2009-2018) was [redacted].

2.3 Analysis of substance function

NPE is present as a critical process agent in four different emulsifiers used at GEHC Bio-Sciences AB Uppsala site, Sweden. The Applicant uses these emulsifiers in the manufacturing of intermediate resins for the further production of more than 120 chromatography products. The following four emulsifiers contain NPE:

- [redacted] (Emulsifier A)
- [redacted] (Emulsifier B)
- [redacted] (Emulsifier C)
- [redacted] (Emulsifier D)

The chromatography resins manufactured by the Applicant are extensively used in the biopharmaceutical industry for the manufacture of biological API's. Furthermore, use of these products in analytical chromatography represents a separate important use, in which mostly gel filtration chromatography resins are used.

The chromatography resins manufactured by the Applicant are for the here concerned products porous biopolymer-based particles (beads). The main product differentiators are particle size distribution, particle porosity parameters and chemical functionalisation of the particle surface. Specific combinations of these properties make up the final resin product attributes that are critical for customers' applications. The NPE-containing emulsifiers are used in the production of resin intermediates, which correspond to the porous particle state prior to specific chemical

[1] Calculated with an exchange rate of EUR 1 = USD 1.1609 (as of September 3rd, 2018).

modification of particle surface. The 120 final resin products are derived from 13 different resin intermediates which are all dependent on the use of NPE-containing emulsifiers. The aim of the project for replacement of the emulsifiers containing NPE is to develop and implement a one-to-one alternative into the manufacture of the existing resin intermediates, and therefore the project will not deliver any new end-products. The existing end-product specifications will not be altered. However, customers will have to be notified about all changes made in the manufacture of the chromatography resins, as the replacement of the NPE-containing emulsifiers will constitute a major modification. In this notification, the Applicant needs to submit information on the emulsifier replacement to confirm that this change has been made with minimal impact on the end-product properties and customer applications. More details on customer notifications can be found in chapter 3.4.

2.3.1 About chromatography and chromatography resins

Chromatography is an essential technique used for separation of mixtures (including, for example, purification processes). The principle behind this technique is the separation of the mixture/solution components by exploiting the differences in the properties of the molecules which are present in the solution. The solution to be separated is dissolved in a mobile phase, i.e. a fluid/solvent, which carries the solution through another substance/material, liquid or solid, called the stationary phase. The various constituents of the mixture interact differently with the stationary phase due to differences in bonding properties, molecular size, and charge, among other properties, and, therefore, travel through the stationary phase at different speeds, allowing their separation (1). The chromatography resins constitute the stationary phase in this process. Examples of chromatography resins as supplied by the Applicant are shown in Figure 3.

Figure 3: Examples of resin products and their application use in terms of large-scale column preparation of chromatography resins for biomolecule purification process

Chromatography resins are extensively used in the biopharmaceutical industry for the manufacture of biological API's such as recombinant proteins, insulin, vaccines, viruses, monoclonal antibodies and blood plasma derivatives. In addition, they are also used in academic research and the food & beverages industry. In the case of academic research, NPE-dependent chromatography resins are used in drug research, whereas in the food industry they are used in food analytics (e.g. to detect food additives).

An example for the use of resins in the biopharmaceutical industry is when scientists modify the DNA of bacteria and other cells to produce biomolecules like insulin, monoclonal antibodies and vaccines through recombinant technology. For these applications, cells are harvested in a reactor under specific growth conditions. When the cells have been growing in the bioreactor tank for a pre-defined time, workers will load the resulting mixture containing the target biomolecule and contaminants onto a special cylinder, or column, filled with the chromatography resins. Some molecules interact more strongly with the chromatography resins and are therefore "slowed down" while flowing through the column, while those molecules that do not interact as strongly flow more freely and are eluted first. By exploiting the differences in electric charge, size and affinity to water and oil of different substances, it is thus possible to separate different compounds from a complex mixture and select for target biomolecules (Figure 4 and Figure 5). Figure 5 below shows a schematic of the agarose chromatography resin-molecule interaction, in which it can be observed that smaller molecules can diffuse into the agarose pore while larger molecules remain in the bulk solution.

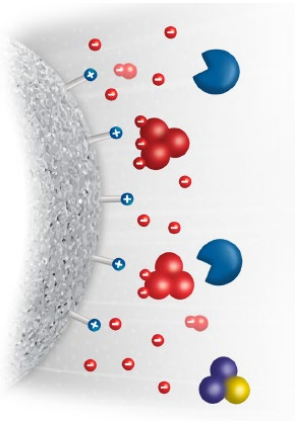


Figure 4: Chromatography resins used as a "workhorse" in commercial manufacturing processes (ion exchange chromatography). In this case, proteins are separated based on differences in surface charge.

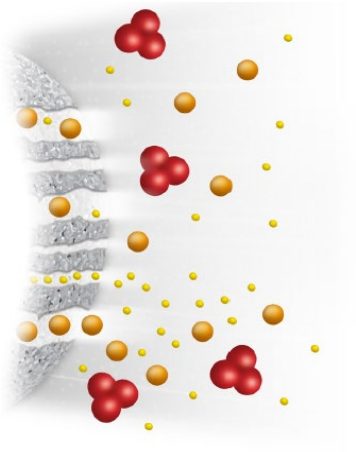


Figure 5: Chromatography resins used for vaccines and/or plasma purification (size exclusion chromatography).

Biopharmaceutical bioprocessing applications

The chromatography resins produced by GEHC LS are extensively used in the biopharmaceutical industry, e.g. to manufacture and purify biopharmaceuticals such as recombinant proteins, insulin, vaccines, monoclonal antibodies and blood plasma derivatives.

The use of chromatography resins leads to better productivity and process economy in the development of biopharmaceuticals. Beaded chromatography resins separate complex biomolecules based on, e.g. their size, charge, hydrophobicity or affinity properties. The separation is dependent, among others, on the attached ligands and porosity properties of the beaded chromatography resins. The offering of beaded chromatography resins is based, e.g. on particle size, pore size distribution, pore structure, pore connectivity, chemical composition, ligands and ligand distribution and density. Based on the target biomolecule properties, the optimal beaded chromatography resin is chosen by the biopharmaceutical customers.

The separation profile of the complex biomolecules is a combination of multiple interactions between attached ligands on the particles, mass transfer effects, and chemical interactions with the particle itself. This means that each beaded chromatography resin has unique properties leading to specific separation profiles of the complex biomolecules to be purified. In many cases, the exact separation mechanism at a sub-molecular level is not known in detail due to the complexity of most biomolecules. Depending on the manufacturing process design, small differences in the characteristics of beaded chromatography resins, can cause challenges for biopharmaceutical companies. Small differences can be caused, for example, by lot to lot variation, although still within product specifications. In some approved biopharmaceutical processes, the beaded chromatography resin is also used to separate and purify biomolecules using product parameters not measured and defined in the product specifications. Consequently, it is very challenging to replace a beaded chromatography resin by an alternative resin without affecting the whole manufacturing process of the biological APIs and thus without possibly altering the quality, purity, safety, and efficacy of the purified biological APIs. These

attributes are of vital importance in the production of biopharmaceuticals used as human therapeutics. This is one of the regulatory hurdles and barriers for any changes made to already approved and registered manufacturing processes of biopharmaceuticals, in whose chromatography resins sold by GEHC LS are used in the purification and separation steps.

While the mechanism-of-action of a variety of chromatography resins may vary with the application, their generic function is to enable separation of the therapeutic biomolecules from a complex biological system. In modern biopharmaceutical industrial settings, beaded chromatography resins are used in purification processes, handling kilograms of biomolecules. A typical purification train may involve a number of serial chromatography steps, where beaded chromatography resins are used for different types of separation purposes, such as binding target biomolecules, separating groups of target biomolecules or removing impurities Figure 6.

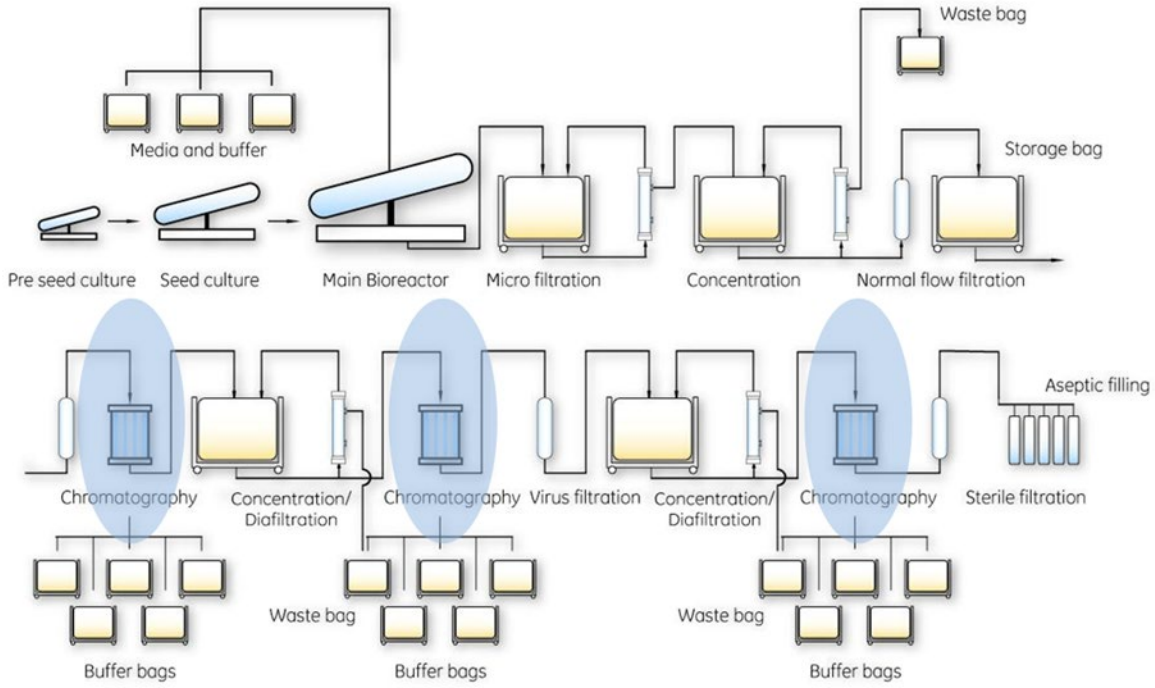


Figure 6: Example of generic flow scheme for the manufacturing of biopharmaceuticals with highlighted area (blue) for chromatography applications

Analytical chromatography applications

Analytical chromatography represents a separate important use of GEHC LS's chromatography resins. Even if the GEHC LS' s chromatography resins used in modern applications have sometimes been replaced by other high-resolution beaded chromatography resins having different properties, both industry and academia have, for a number of decades, designed characterization and analytical methods for biomolecules using GEHC LS's chromatography resins. This is also the main reason for the high number of scientific publications and review articles referring to the use of GEHC LS's chromatography resins for analytical chromatography.

2.3.2 GEHC LS's manufacturing process of chromatography resins

The main steps of the manufacturing process scheme for intermediate resins, also called base matrices, is illustrated in Figure 7.

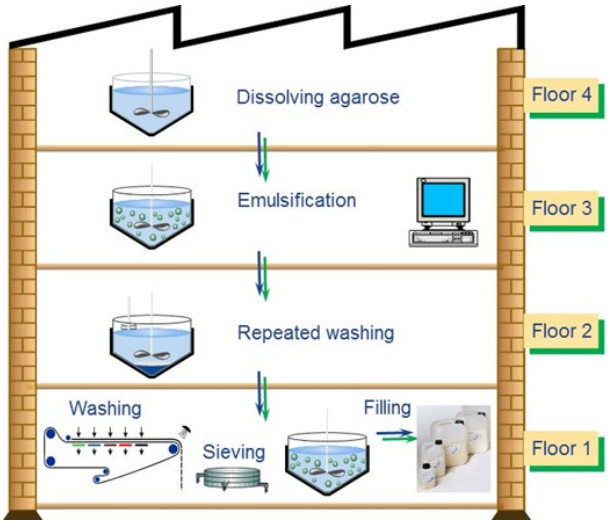


Figure 7: Process scheme for the manufacture of intermediate resins, so called "base matrix", for agarose-based base matrices.

Since the porous particles originate from an emulsion, they are formed suspended in an organic solvent phase that needs to be removed. The process steps after the emulsification are a series of washing steps that serve to ensure that all residuals emulsifiers, byproducts, and solvents are removed. The washed particles correspond to an intermediate resin product (so called base matrices), which is then ready for further processing, mainly in terms of chemical modifications. Particle size distribution is a very important product attribute of chromatography resins, and process techniques and emulsion design have therefore been developed to provide particle size control. NPE-containing emulsifiers are used because of their excellent emulsifying and emulsion stabilizing properties, which thereby offer very good control of final particle size distribution. In terms of emulsification process technology, both stirred reactor systems and colloidal mills can be used, depending on the targeted particle size and particle size distribution. The fact that NPE-containing emulsifiers are also compatible with these type of process technologies contributes to make them very suitable emulsifiers for the intermediate resin manufacturing.

Functional descriptions for NPE-containing emulsifiers in the manufacturing process of resin intermediates are outlined in Table 2.

The use of NPE-containing emulsifiers as a component is critical for ensuring the functionalities of the emulsifiers containing this component. These emulsifiers should be considered as processing agents, that are removed during the manufacturing process, and are thus not part of the final chromatography resins. The primary functions of the emulsifier are:

droplet-break up facilitation, droplet formation, and stabilization of droplets-particles during the cooling phase (see Table 2 for further information). The details of the process schemes, and handling within individual steps, are not the same for all concerned emulsified products or system groups. In general, however, the primary functionalities mentioned above are crucial for all emulsifiers. A generalized substance function description for the emulsifiers containing NPE as used in the present processes can be found in section 2.3.3.

Table 2: Functional descriptions of emulsifiers containing NPE.

Process operation	Process aid function of NPE-containing emulsifier	[redacted]
Solvent phase preparation	To become solubilized in hot solvent solution phase.	[redacted]
Emulsion formation	Reduce interfacial tension between an aqueous agarose phase and the organic phase, and thereby facilitate emulsion droplet formation with low defect contents (droplet formation).	[redacted]
Emulsification efficiency	To facilitate the droplet size-reduction emulsification process to reach targeted drop size distribution (DSD).	[redacted]
Stabilization (particle formation)	To stabilize droplet during cooling and particle formation to minimize particle defects (stabilization of droplets-particles).	[redacted]
Washing	To be removed from base matrix resin. Low interference of emulsifier residues with process conditions.	[redacted]
Other	Other ways by which the emulsifier substance influence process and product quality.	[redacted]

An alternative emulsifier must meet all of the described key functionalities before it can be considered for further development, testing and scale-up. A robust and reliable

product quality is mandatory for the chromatography resins supplied by GEHC LS, especially when it comes to the use in the industrial manufacturing process of the biological API's. The quality, purity, safety, and efficacy of the purified biomolecule must be ensured.

Additionally, the following aspects of large-scale emulsion manufacturing where emulsifiers containing NPE are used present challenging technical process conditions:

i. The emulsified phase (aqueous solution containing the substance making up the intermediate resin, e.g. agarose) is significantly more viscous than the continuous solvent phase. This viscosity condition makes the droplet break-up process of emulsification challenging, and typically processing requires longer lead times and higher energy input.

ii. The same aqueous phase also contains, organic and inorganic residuals, that are surface active. The variability of these residual contents presents a functional challenge to some emulsifier chemistries.

iii. Processing must be performed at an elevated temperature due to the thermo-gelling properties of some biopolymers used, e.g. agarose. At these temperatures most solvents offer very good solubilization of emulsifiers, which limits the choice of emulsifiers. De facto, the emulsifier must solubilize in the solvent phase at the temperature used during the process.

iv. After emulsification, emulsion processing also involves cooling, under which robust emulsion stability must be maintained. Therefore temperature-stability of emulsifier function is required for a large temperature range.

v. After cooling and subsequent particle formation, the suspension must present physical properties that enable efficient washing processing, so that all residues such as solvent and emulsifier can be removed.

The aim of the project for replacement of emulsifiers containing NPE is to develop and implement a one-to-one alternative to the present emulsifiers used in the resin design and manufacturing. Currently, no alternative emulsifiers are available that could provide equivalent functionalities.

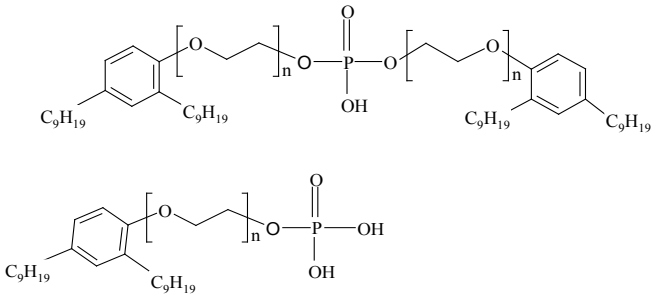
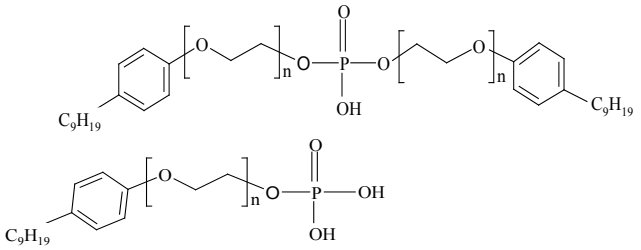
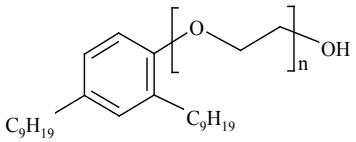
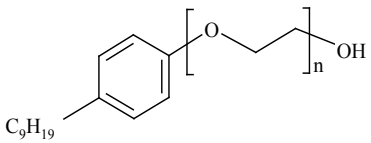
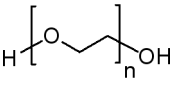
2.3.3 Chemistry of emulsifiers containing NPE

The Applicant uses four different emulsifiers that contain NPE. These correspond to complex mixtures of several different surface-active substances, where phosphate-esters make up the dominating fraction. In a simplified overview of the chemistry of the emulsifiers, the main difference is found in:

- the relative content of di- to mono-phosphate ester
- content of ethoxylated NPE that are not covalently linked to phosphate ester

- the content of acidic groups
- the degree of polymerization of the ethoxylated part of the ethoxylated NPE

Table 3: Structure of compounds being components of the 4 emulsifiers in scope.

Compound	Structure
Phosphate esters of ethoxylated dinonylphenol	
Phosphate esters of ethoxylated nonylphenol	
Ethoxylated dinonylphenol	
Ethoxylated nonylphenol	
Polyethyleneoxide	

2.4 Market and business trends for the use of NPE-containing emulsifiers

2.4.1 Financial information

In 2017, the total annual turnover of GEHC Bio-Sciences AB facility in Uppsala amounted to EUR 1,571 million. Figure 8 shows the evolution of the Applicant´s turnover between 2014 and 2017.

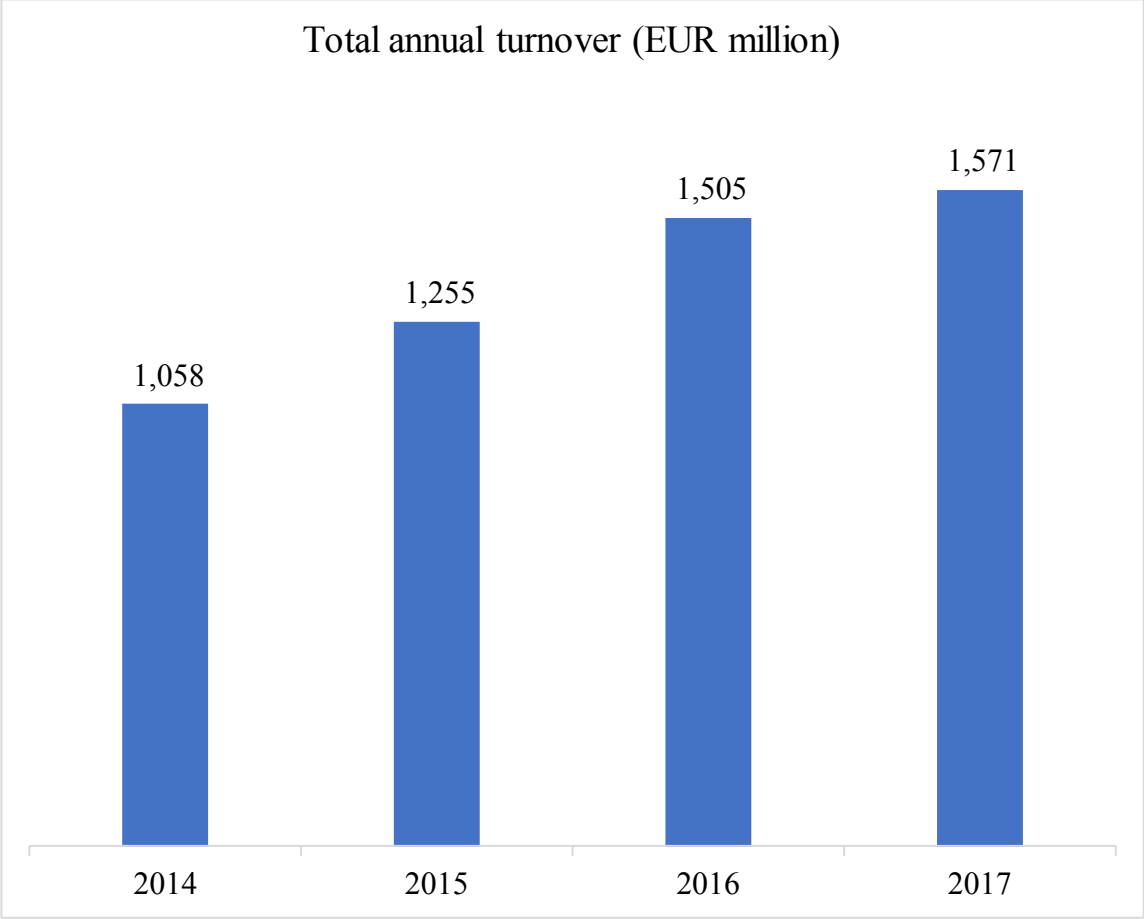


Figure 8: Applicant´s Turnover 2014-2017.

NPE-dependent chromatography resins are responsible for [redacted] of GEHC Bio-Sciences AB's Uppsala facility turnover. In 2017, for example, [redacted] of the Applicant´s annual turnover was related to NPE-dependent chromatography resins (see [redacted]).

[redacted] shows the annual turnover generated by the sales of NPE-dependent chromatography resins between 2015 and 2017.

	2015	2016	2017
Turnover related to NPE-dependent chromatography resins (EUR million)	[redacted]	[redacted]	[redacted]

Considering the period between 2014 and 2017, the average operating profit margin related to NPE-dependent chromatography resins sales was approximately [redacted]

2.4.1.1 Supply chain

Chromatography resins are produced by the Applicant and mainly sold to various industrial and academic clients from the biopharmaceutical sector, academia and food industry. GEHC Bio-Sciences AB has also some distributors which supply the market with GEHC LS's chromatography resins, mainly in small quantities. Sales revenues related to distributors account approximately [redacted]. Bulk sales are made directly by GEHC LS. Figure 10 presents the Applicant´s supply chain of NPE-dependent chromatography resins.

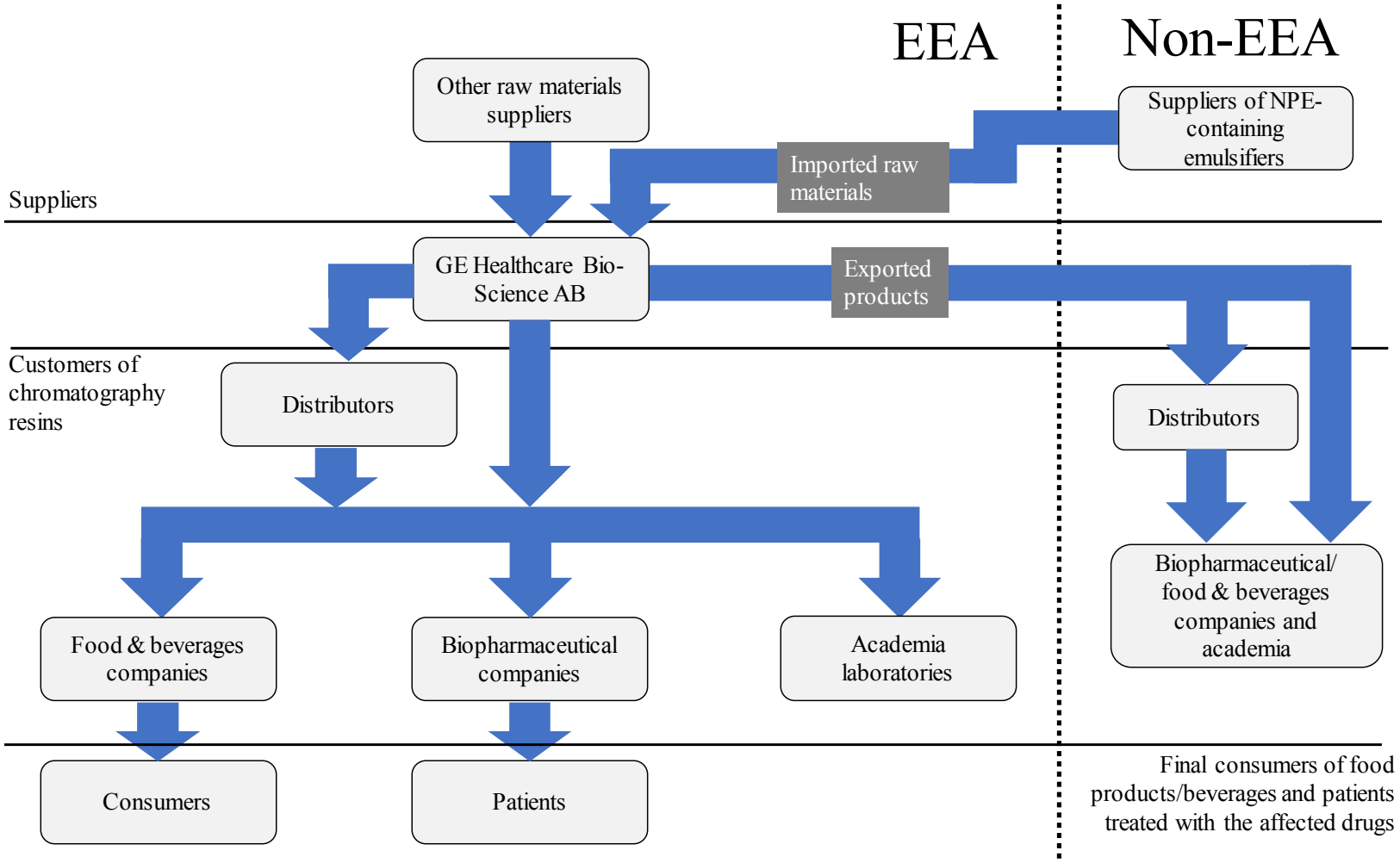


Figure 10: GEHC Bio-Sciences AB supply chain for NPE-related chromatography resins

As shown in Figure 10, the Applicant's supply chain for NPE-related chromatography resins comprises the following actors:

- **GEHC Bio-Sciences AB** purchases NPE-containing emulsifiers from one supplier located within EEA.

- **Other raw materials suppliers.** Other raw materials are necessary to produce chromatography resins. These are mainly solvents, used for washing of the porous intermediate resins and the end-products, agarose, allyl dextran, cellulose, bisacrylamide, -and crosslinkers used in the manufacture of the porous intermediate resins and other chemicals used in the manufacturing processes for surface modification of the porous intermediate resins. Suppliers/manufacturers/distributors of these other raw materials are mostly located in the EEA.

- **Customers.** Customers of GEHC Bio-Sciences AB are biopharmaceutical companies, academia and food & beverages industry. Distributors sell GEHC LS's chromatography resins in small volumes.

- **Public / patients.** Biopharmaceutical companies sell their products (human therapeutics and vaccines) to the public/patients. Biopharmaceutical companies use GEHC LS's chromatography resins in the manufacturing processes of these products. They have approved and registered manufacturing processes of biological APIs using these chromatography resins. At least 190 human therapeutics and vaccines are manufactured using GEHC LS's chromatography resins. These human therapeutics and vaccines cover widespread therapeutic areas such as: diabetes, anaemia, haemophilia, blood coagulation factors, rheumatoid arthritis, psoriatic arthritis, growth hormone deficiency, fertility, leukaemia, hepatitis, ulcerative colitis, psoriasis, thrombocytopenia, myocardial infarctions, HAE attacks, meningitis, neuroblastoma, myocardial infarctions, influenza, immunosuppressive treatment before transplantation, wet AMD and various other rare diseases. The human therapeutics and vaccines are intended for treatment of millions of patients all over the world with serious, possibly life-threatening diseases.

2.4.2 General market information and future market trends about chromatography resins (2)

In 2016, the worldwide chromatography resins market was valued at [redacted]. The chromatography resins market is expected to grow at a CAGR of [redacted] during the period 2017-2025 because of the [redacted] academic and commercial R&D investments on biopharmaceuticals development.

Looking at the market segmentation by end-use of the chromatography resins, biopharmaceutical & biotechnology is the [redacted] segment which represented [redacted]

[redacted] in terms of revenue in 2016. This is because of the high consumption of chromatography resin in biopharmaceutical processes. In the case of food & beverage, revenues amounted [redacted] in 2016.

The global market of chromatography resins is driven by:

- drug discovery research by biopharmaceutical companies and contract research organizations (CROs)
- the expected rise on global healthcare expenditure (increased demand for medicines which consequently require more chromatography resins to be used in pharmaceutical production);
- the growth of the biopharmaceutical industry, which, is likely to result in the increasing demand for chromatography resin. This growth is mainly driven by the increase in the occurrence of chronic diseases and disorders;
- the increasing number of Contract Manufacturing Organizations (CMOs) and CROs around the world, which are major consumers of chromatography resin;
- the expected increase on demand for chromatography resins in food safety and quality control applications. Chromatography technique is used for many applications in the food and beverage industry; some of which are amino acid analysis, detection of aflatoxin in food, vitamin separation, analysis of colorants and residue, profiling various food components, triglyceride, and sugar content analysis. Until now, mainly sublimation, evaporation, distillation processes were used for separation application in the food and beverage industry, but the added benefits of chromatography over conventional techniques have recently triggered the demand for chromatography resins;

Europe is the second largest market for chromatography resins both in terms of volume and revenue. The European chromatography market represented [redacted] in 2016. At Member State level, [redacted], because of the significant presence of research and development facilities of global pharmaceutical companies in this country.

The GEHC LS facility in Uppsala commercialize its NPE-dependent chromatography resins worldwide. Of the NPE-dependent chromatography resins manufactured at the Applicant´s site, 60 % are exported to non-EEA countries. More than 90 % of its NPE-dependent chromatography resins are exported outside Sweden. At the national level, GEHC Bio-Sciences AB is a strong contributor to Swedish export, with revenues representing 0.3 % of the Swedish GDP and approximately 1 % of the overall Swedish export. The Applicant expects a market growth in the upcoming years for all downstream markets (biopharmaceuticals, food & beverages and academia), in line with the drivers for the growth of the global chromatography resins market.

The biopharmaceutical sector is highly regulated/monitored [e.g. in Europe by the European Medicines Agency (EMA) and in USA by the US Food and Drug Administration (FDA)] and therefore it is very difficult and challenging for biopharmaceutical companies to make changes

in their approved manufacturing processes, such as changes of chromatography resins since these resins are a critical part of the manufacturing processes of biological API's. Apart from the chromatography resin performance, this sector also requires consistent product quality and supply chain sustainability (security of supply).

The academia market for chromatography resins is mainly driven by need of products with low prices and consistent product quality. The growth of this market depends on the academic funding from major bodies which have historically increased and are expected to continuously grow in the future.

The food & beverage sector is mainly driven by need of products with low prices and specific regulatory requirements (e.g. regulatory requirement from the European Food Safety Authority-EFSA).

GEHC LS's NPE-dependent chromatography resins are unique and there are not any other chromatography resins with exact equivalence neither within the greater GEHC LS portfolio nor on the market. Competitors to GEHC LS only produce similar, but not equivalent products, meaning these products cannot directly replace GEHC LS's chromatography resins in customer's manufacturing processes of biological API's without going through an extensive requalification/reapproval of the manufacturing processes).

2.5 The Applicant annual tonnage use of NPE

Emulsifiers containing NPE are used at a single manufacturing site in Uppsala, Sweden. Taking into consideration the use average between 2010 and 2018, the amount of emulsifier used per year was approximately [redacted], with quantities of NPE content being approximately [redacted]. Considering future sales growth and the worst-case of failure in the plans to substitute the use of NPE-containing emulsifiers, a maximum usage of up to [redacted] of NPE-containing emulsifiers ([redacted] of NPE per year) is forecasted to be used at some point during the 12-year review period. Therefore, the overall tonnage considered for the risk assessment is [redacted] per year, which is a worst-case scenario and upper limit.

2.6 Environmental impacts of the applied for use scenario

2.6.1 Methodological approach

The assessment of environmental impacts derived from NPE releases presents important challenges due to the uncertainties regarding the effects of NPE (and endocrine disruptors in general) at different concentration levels of exposure.

Given the above, the assessment of any potential environmental impacts related to the use of NPE requires the use of qualitative information combined with alternative quantification methods.

2.6.1.1 Suggested approaches to perform the assessment: advice from a paper published by ECHA

For OPnEO and NPnEO, i.e. NPE, ECHA published the article "SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO" (SEAC/37/2017/03) (2) which provides suggestions about possible approaches to be followed in the assessments conducted in the SEA.

According to ECHA's description, it is important to recognize that the full quantification of both benefits and risks is not mandatory under REACH, and that a mixed qualitative and quantitative SEA can be used to demonstrate that the benefits of the continued use of a substance outweigh the risks (2). Indeed, ECHA further states that in some cases a qualitative assessment can be sufficient when the benefits to society from continued use are considerable and the environmental emissions are properly controlled. Costs for additional risk management measures that could be implemented or currently in place are not relevant for the assessment; however, ECHA states that such costs can be provided to justify releases, by demonstrating that releases are minimized as much as possible both technically and practically (2).

The main suggestion provided by ECHA on how to conduct a SEA in the case of endocrine disrupting substances (specifically OPnEO and NpnEO) is that *"...monetize benefits of continued use and quantified release estimates, complemented with qualitative information, form the basis of a semi-quantitative approach to justifying that the benefits of continued use outweigh the risks."* ((2), page 2).

Besides the monetised estimate of the benefits of continued use of a substance (which have commonly been provided in the previous AfA), ECHA states in its paper from November 2017 (2) that the following information seems to be necessary to be included in the AfA:

- *"quantified release estimates accompanied with a qualitative description of where the releases occur (e.g. dilution capacity of a river and number of release sources and their temporal and geographical distribution)"* ((2), page 2);
- *"a qualitative description of the potential impacts (e.g. on fish populations)"* (((3) , page 2).

In ECHA's opinion, the information listed above should be sufficient to qualitatively conclude whether the benefits of a continued use outweigh the risks. However, still according to ECHA (44), further contextual information on the likelihood and significance of potential impacts can be provided to support the case - *"e.g. the margin of safety between predicted or measured environmental concentrations and relevant thresholds of exposure/adverse effect in biota or quality standards from other legislation"* ((2), page 2). A qualitative comparison of benefits and risks explaining why, from a societal perspective, it is better to continue the use of the substance should be performed by the Applicant.

ECHA has declared that *"any benchmarks (e.g. € of reducing kg of release) above which an authorisation would always be granted cannot be set"* ((3) , page 3). A magnitude of such a

benchmark has been reported in the form of a range for PBT/vPvB substances in the SEAC PBT approach (2), however ECHA notes that such benchmark cannot be directly transferred for use in the case of endocrine disrupting substances.

Despite the fact that ECHA states that such ranges cannot be directly applicable to the case of endocrine disruptors, since the use of only qualitative information is always open to subjective interpretations, the benchmark ranges derived in the paper about PBTs/vPvBs will be used in this SEA at least as an auxiliary measure for the assessment (see the following section).

2.6.1.2 Efforts made by the Applicant to monetize environmental impacts of endocrine disrupting substances: taking advantage of the PBT and vPvB case to derive an auxiliary monetised value of impacts

Due to the issues surrounding the assessment to endocrine disruptors and NPE specifically, alternative methods for evaluating the environmental impacts need to be considered. Taking into account the existing limitations to an ecosystem services valuation and other preferred methods, an auxiliary estimation for environmental impacts caused by endocrine disrupting substances can be based on a cost effectiveness method which ECHA discussed for PBT and vPvB substances (2).

A PBT/vPvB benchmark study by the Vrije Universiteit Amsterdam (VU) (4),which is referred to by ECHA as a useful source of information for the topic (5) is used here as an initial basis for the analysis. This assessment was conducted by VU with the aim to develop a benchmark for regulatory decision making under REACH restriction and authorisation processes of PBT and vPvB substances under the premise that in order to decide whether a regulatory action results in net benefits for the society, it is useful to have a comparator or benchmark which reflects the amount of costs that are considered to be worth taking for the reduction of PBT and vPvB.
As ECHA has already acknowledged, due to the specific properties of substances such as PBTs and vPvBs, a full cost-benefit analysis is not always feasible. Therefore, a cost-effectiveness analysis is in some cases more appropriate (5). For the case of NPE there are several difficulties revolving around the lack of different type of data necessary depending on the approach used such as the lack of specific historical data, and the high level of uncertainty a benefit transfer of such data would incur.

The VU assessment project collected information on costs to reduce the stocks, presence, flows and emissions to the environment of eight groups of PBT substances and, where possible, related this information to the final decision making (whether the reduction measure had been implemented or rejected due to excessive costs). The cost levels of rejected measures can provide an indication of the maximum willingness to pay for the reduction of PBTs. This can be considered in the context of NPE due to some similarities in the properties of such substance groups, as well as the conclusion from the VU study which states “once control is included for other influencing factors…the average unit costs per kg seem transferable across substances” for the mean unit costs (4).

The report by VU examines 36 studies from 10 countries spanning 25 years, with approximately 80 % of these being from the EU. Most of these studies were carried out after 2009. In this report, VU considers three main cost categories for environmental improvements (4):

- Substitution costs - which is either the replacement of the substance with another, or the elimination the substance with a new process.
- Emission reduction costs - cases where the use of the substance changed, such as a new process with closed applications that ensures drastically reduced (near zero) emissions and exposure.
- Clean-up costs - also known as remediation costs; VU includes many forms of clean up from the studies ranging from the removal of the substance from the environment to removal of the substance from man-made structures and equipment.
- Other costs – VU notes that each of the examined studies varies in which costs are included or excluded, and that some of the outliers failed to include the 'real cost' due to various factors such as secondary benefits, for this reason among others, the outliers are excluded from the final conclusion.

In the studies reviewed by VU, the range of costs was found to be highly sensitive to outliers due to many factors, primarily a difference in methodology between the studies, such as the exclusion/inclusion of secondary benefits and certain extreme scenarios, e.g. the economic impacts of temporarily closing a high traffic tunnel down as part of clean-up costs. In addition, a pattern of increasing costs with decreasing concentrations of a substance is observed. The below figure is adapted from the VU report. It demonstrates the median costs per kg for the three different cost types, with remediation having nearly double that of emission control.

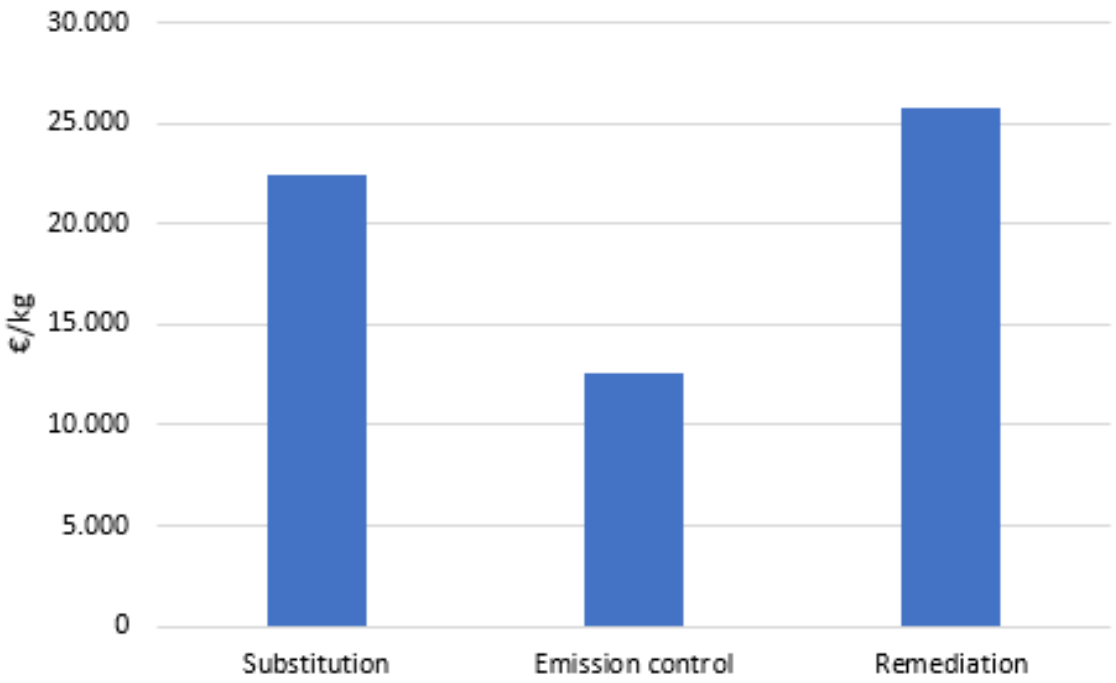


Figure 11: Median unit costs of different cost types, excluding outliers (adapted from (4)).

While the previous figure represents the median cost per kg, in order to conservatively estimate the potential environmental impacts, the upper bound of acceptable cost-effectiveness is of interest for a conservative estimation. VU concludes that the viable range depends on the specific substance and situation, though with a broad 'grey zone' in which the cost-effectiveness per kg is no longer considered acceptable, while there are some outliers. VU suggests that EUR 1,000 – 50,000/kg demonstrates a probable 'grey zone', though VU notes that the range is not based on specific cases but is their general conclusion and that accuracy of this range could be improved with additional data in future studies. This range of a potential benchmark for the cost-effectiveness is demonstrated below in Figure 12.

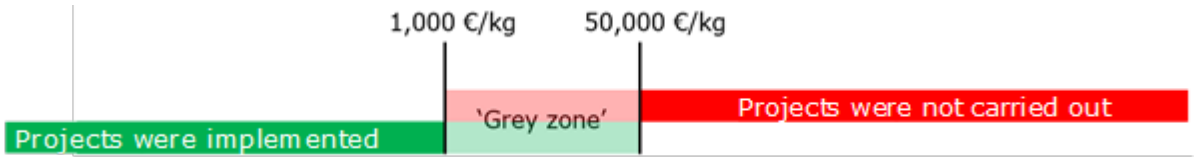


Figure 12: Visual representation of VU's cost-effectiveness `grey zone´ (adapted from (4)).

Despite the fact that no benchmark could be defined by the VU project, VU concludes that the range of the so-called 'grey zone' is the range in which the measures to reduce the use, presence or emission of PBTs may be prohibitive from a cost-effectiveness standpoint, depending on the specific case. As the sample is limited and there are significant outliers, VU emphasizes that the use of this "grey zone" cannot be used as a pass-fail criterion in decision making. However, VU suggested such a grey zone could be used in the benchmarking process as an initial screening for which further situation-specific assessments would be required on a case-by-case

basis. While this grey zone is provided with caution and is based on limited data, it is currently the best estimate for the mean costs that are still considered cost effective, and therefore can be considered as the range for the willingness-to-pay (WTP) related to the impact of these substances (4). VU's linear regression analysis finds "…that the type of substance does not have a significant effect on the mean unit costs…" (4) which further supports the case for the relevance of these figures with the endocrine disruptor NPE.

With this data and range for the estimated WTP for cost-effectiveness per kg, it is important to note that this estimate is provided as a general measure only and should only be used to form an opinion when also considering the qualitative aspects described in this report.

With this consideration, an auxiliary monetised measure of environmental impacts is estimated in this SEA using the range of **EUR 1,000 to 50,000 EUR per kg of NPE emissions**.

2.6.2 Assessment of environmental impacts at the GEHC Bio-Sciences AB Uppsala site

2.6.2.1 Implemented risk management measures and releases

As described in the CSR, multiple risk management measures have been implemented (and continue being assessed for implementation) at in the Uppsala site in order to reduce the emissions of NPE to the environment.

During the entire process, emptied barrels, containers, cans, funnels, gloves and other personal protective equipment (PPE) that have been in contact with NPE-containing emulsifiers are discarded as hazardous waste and incinerated by an authorized third-party waste vendor.

With regards to the WCS 2 (Transfer into smaller containers - PROC 9), measures to improve the handling of NPE-containing emulsifiers in this transfer process, and thereby significantly reduce emissions to on-site wastewater treatment plant (WWTP) from this WCS, have been identified and underway to be implemented. This involves improvement in how the content of the 200 L barrel is transferred to 15 L containers. Currently a stainless-steel valve is used, and it is rinsed, and the washing liquid is released in the process water stream ending into the on-site WWTP. This emission to the water stream will be eliminated by replacing the steel valve with a disposable valve which will be discarded as hazardous waste and incinerated by an authorized third-party waste vendor. From mass-balance estimates for the full NPE lifecycle, it is expected that these improvement in transfer handling routines will lead to an overall reduction of 10% of the yearly NPE emission.

Concerning the WCS 4 (Chromatography resin production - PROC 1), the wash liquid from most of the washing steps is sent for pre-treatment using active carbon filters to adsorb NPE residues. The filtered water that has passed the active carbon pre-treatment is thereafter sent to the on-site WWTP. The purpose of the active carbon pre-treatment is to remove NPE in the outgoing water. The wash liquid from the last washing steps (washing of the vessels) in the

manufacturing process of the resin intermediates, with emulsifier residues below detection level, is sent to the on-site WWTP, see Figure 13.

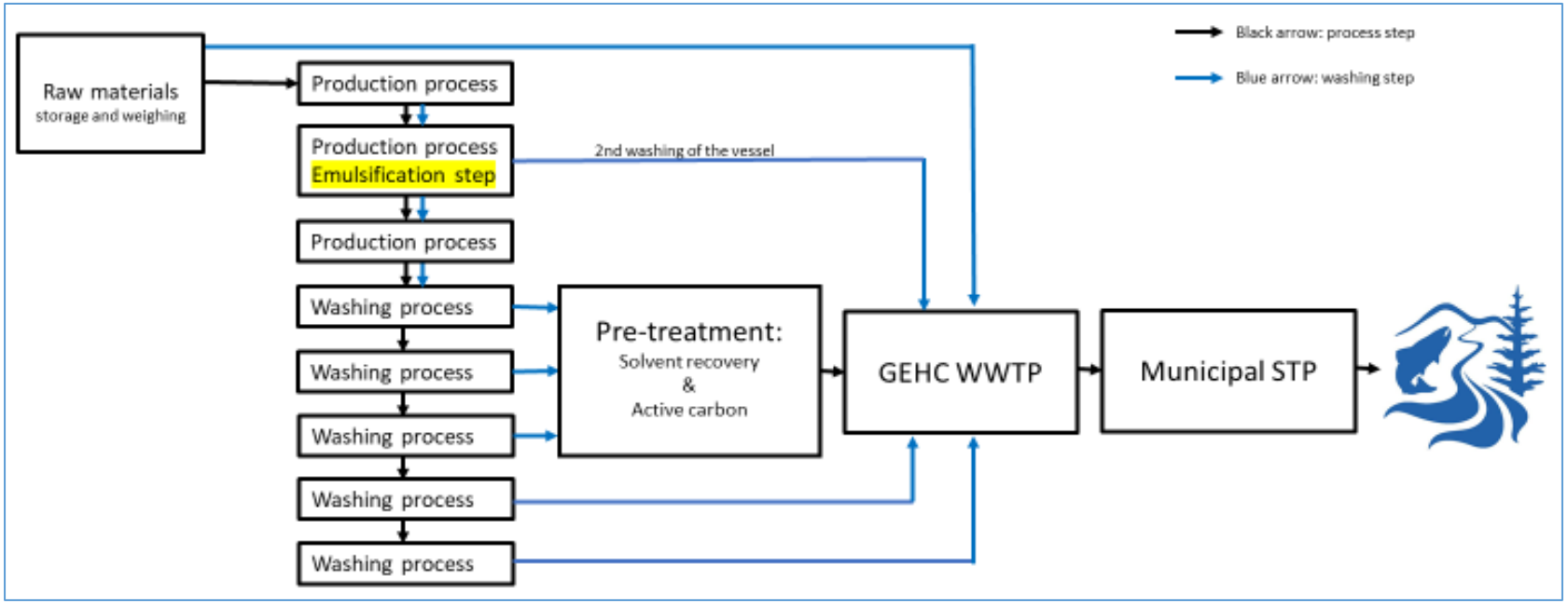
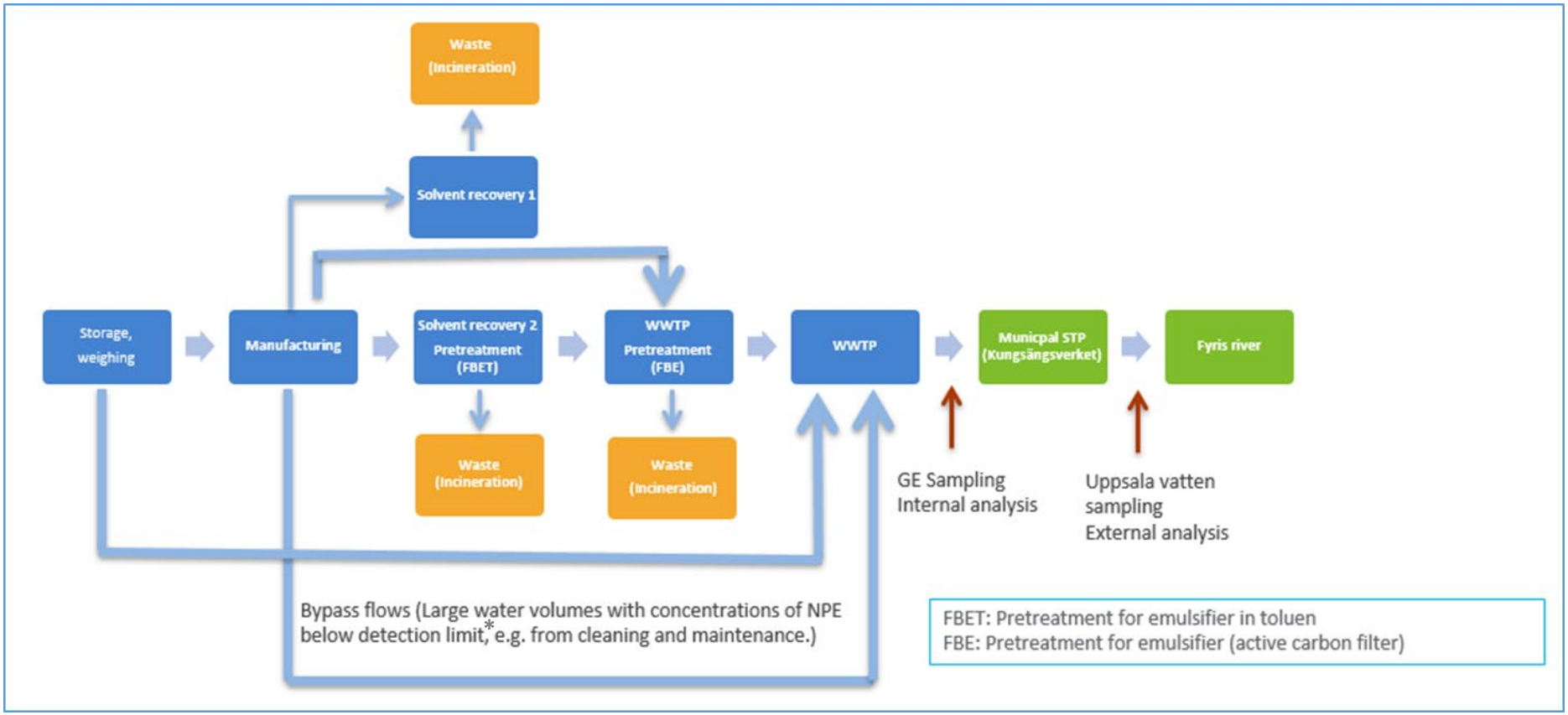


Figure 13: Process and wash process steps.

In consideration to WCS 6 (Process Waste management - PROC 1, PROC 8b), more specifically solvent recovery (LÅV), washing liquids that contain NPE containing emulsifier in toluene are sent to pre-treatment (FBET). Toluene is recycled, and the remaining liquid is sent to pre-treatment for emulsifiers (FBE). Washing liquids with ethanol that may contain NPE are sent to a different mother liquid tank. In this case, a thin film evaporator evaporates solvent from the emulsifier and the emulsifier is then pumped to a waste tank. Waste is incinerated by an authorized third-party waste vendor. Specifically concerning the pre-treatment for emulsifiers (FBE), the process water is pumped from the reaction vessel to the on-site WWTP, closed system performed by pumps. Active carbon is added, and the slurry is blended, which makes the nonylphenols adsorb on to the active carbon. Thereafter, the active carbon is filtered out and the water is lead to the biological treatment at the WWTP. The effectiveness of the pre-treatment is 99%. Semi-drying is performed within the filter containing the active carbon (Fundabac-filter model) with compressed air and the semi-dried active carbon (with the adsorbed nonylphenols) is released into a collection-bag. This bag is thereafter sent for incineration by an authorized third-party waste vendor.

After the aforementioned processes and pre-treatments, nonylphenols accumulate in the sludge in the bioreactors in the WWTP. The retention time is indeterminate but eventually the nonylphenols are released to the municipal sewage system and WWTP (Kungsängsverket), ultimately being discharged to the Fyris river, see Figure 14.



* Detection limit: 0.1mg L-1

Figure 14: NPE lifecycle.

As shown in the CSR, identified emissions of NPE occur via wastewater and the current total release of NPE in effluent out of the on-site WWTP is approximately [redacted] considering 365 operating days.

An environmental report from 2016 published by the Uppsala STP (6) advises that, from a total annual incoming sludge of 3,260 metric tonnes, the NPE content reaches approximately 29 Kg/year. The same report shows that the amount of total emissions of alkylphenols and ethoxylates to the Fyris river sums up to 1.9 Kg/year. Considering the emissions from the applicant's plant back in 2016 ([redacted]/year) and the measured NPE content at the municipal STP in that year, it can be estimated that the Applicant is responsible for approximately [redacted] of the NPE emissions in the STP. Applying this ratio to the amount of alkylphenols and ethoxylates found in the Fyris river (1.9 Kg), the Applicant might be responsible for [redacted] of this content (assuming that the treatments applied at the Uppsala STP are not able to reduce at all the amount of NPE that ends up in the Fyris river, what is a very worst-case scenario). Details about the discharge rate of the effluent and Uppsala STP as well as the receiving surface water flow rate are available in the CSR.

Due to potential market demand growth and in the worst-case that substitution efforts face difficulties (or fail to implement an alternative as planned), the usage of NPE may increase until an alternative substance can be used (up to [redacted]) and therefore NPE emissions from the site may increase depending on the success of NPE substitution (up to [redacted] in the worst-case during the review period). Following a conservative approach, the environmental impact assessment performed in this SEA will therefore take into consideration worst-case scenario in which the substitution plans face difficulties or fail and emissions from the on-site WWTP are a maximum of [redacted] NPE/year.

It is important to note that this assessment will show highly overestimated environmental impacts since, even if the substitution efforts fail, the Applicant would not use [redacted]/year of NPE every year of the applied review period. Such usage (approximately three times the current amounts) can most likely only be reached in the last year of the applied review period and only if substitution fails.

2.6.2.2 Investments for implementing risk management measures to reduce NPE emissions

Since 2007, the Applicant has made significant investments to reduce its NPE emissions.

Investments for a new on-site WWTP have been made in 2007 at a cost of [redacted][2]. In addition, two additional investments summing up to [redacted]

[2] Converted using a rate of SEK 10.5806 per 1 euro as of September 3rd 2018.

[redacted] have been made by the Applicant in the systems used for pre-treatment of NPE.

2.6.2.3 Derivation of an auxiliary monetary value for the environmental impacts based on the volume of NPE emissions

Taking into consideration that the amounts in EUR per kg of emission provided in the paper from the VU in Netherlands are described in a range, the calculations of an auxiliary monetary value for the environmental impacts due to the emissions of NPE from the Applicant's site will also be performed in the terms of a range, see Table 5.

Table 5: Derivation of an auxiliary monetary value for the environmental impacts based on the volume of NPE emissions.

Maximum volume of emissions per year (in Kg) assuming a 12-year review period	[redacted]	
	Lower bound	**Upper bound**
Range provided in the VU study (in EUR per kg)	1,000	50,000
Total amount in EUR given the level of emissions reported for the relevant assessed site per year	[redacted]	[redacted]

The annual monetised amounts (lower and upper bounds in EUR) which refer to the maximum level of emissions per year can be used to calculate the monetised amounts across the 12-year requested review period, see Table 6.

.

Table 6: Derivation of an auxiliary monetary value for the environmental impacts across the 12-year requested review period.

2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
[redacted]											
NPV in EUR in 2021 (lower bound) (using a 4% annual discount rate)											[redacted]
[redacted]											
NPV in EUR in 2021 (upper bound) (using a 4% annual discount rate)											[redacted]

Since the ranges calculated in this section cannot be used as the only reference for final conclusions on environmental impacts (but only as an auxiliary value to support the analysis), a final assessment (also using qualitative information previously disclosed) is performed in the following section.

2.6.3 Conclusions on environmental impacts in the applied for use scenario

In view of the risk management measures in place at the Applicant's production facility (collection of NPE waste, disposal by incineration as hazardous waste by a licensed contractor, pre-treatment with active carbon, biological treatment of wastewater), emissions of NPE to the aquatic environment are effectively minimized. However, elimination of NPE in wastewater treatment is not complete, but may result in formation of intermediate metabolites and ultimately 4-tert-nonylphenol. The only pathway releasing NPE to the aquatic environment is in the wastewater from on-site WWTP (a maximum of [redacted] per year and [redacted] over 12 years), resulting in monetised environmental impacts ranging between [redacted]).

3 SELECTION OF THE "NON-USE" SCENARIO

3.1 Efforts made to identify alternatives

The Applicant started Research and Development (R&D) efforts for substituting emulsifiers containing NPE in 2003. R&D work at GEHC Bio-Sciences AB towards the replacement of emulsifiers containing NPE has made use of the open literature and past industrial experiences by adopting an established structured approach for the identification of alternatives and by cross-examining the results against the outcomes and recommendations from related programs. The "post-change" chromatography resins manufactured with an alternative emulsifier and/or manufacturing process must as far as possible be interchangeable with the "pre-change" chromatography resins produced with NPE containing emulsifiers.

The Applicant is following a two-options approach for the identification of possible alternatives:

- Replacement of the NPE containing emulsifiers by an alternative emulsifier in the manufacturing process of the intermediate resins using current manufacturing technology.
- Alternative manufacturing technologies for the manufacture of the intermediate resins.

3.1.1 Efforts made to identify alternatives: Replacement of current emulsifiers by an alternative emulsifier

A research program for identifying new emulsifier candidates to replace the NPE-based emulsifiers due to environmental concerns was initiated in 2003-2004 internally. Since then, the Applicant has carried out numerous R&D activities to identify suitable alternatives. However, no robust alternative has been identified so far. Currently, four potential alternatives from the group of phosphate-based esters are being investigated. An overview on their properties is described in section 3.3. Additionally, in 2016, the *Statens Provningsanstalt* (SP) Technical Research Institute of Sweden was contracted to perform a study to screen emulsifier candidates.

In 2016, GEHC Bio-Sciences AB has submitted an AfA for the use of 1,2-Dichloroethane (EDC), which is also used in the manufacture of porous particles based on a polysaccharide (dextran) for the production of a separate product portfolio of chromatography resins. The Applicant is also undergoing extensive R&D and manufacturing programs for identifying and fully implementing an alternative to EDC, in addition to the activities for substitution of the emulsifiers containing NPE.

3.1.1.1 Initial Screening

The long-term goal of the NPE Replacement project is to deliver replacement solutions to the following emulsifiers containing NPE which are currently used in the production of several base matrices further used in the manufacture of numerous end-product chromatography resins:

- [redacted] (Emulsifier A)
- [redacted] (Emulsifier B)
- [redacted] (Emulsifier C)
- [redacted] (Emulsifier D)

Key activities include:

- Set the base line of critical product performance characteristics for base matrices produced using existing NPE-containing emulsifiers. This activity involves analytical method development and extensive sampling and characterization of present process and base matrices;
- Identify and implement new emulsifier replacement candidates;
- Verify equivalent properties and performance on base matrices and selected end-products using the new selected emulsifiers;
- Validate the new base matrix processes and selected end-products;
- Release customer notifications.

As discussed in chapter 1, this project will not develop any new end-products but replace the emulsifier/emulsification system in several existing emulsification processes. The relevant product portfolio consists of more than 120 end-product chromatography resins used in different applications. The objective is to perform the process changes without affecting end-product properties (specifications), end-product performance or any existing end-product claims.

The extensive program initiated in 2003-2004 examined more than 100 commercially available emulsifier candidates to gain an idea of which emulsifiers may work in large-scale emulsifications. A full list of considered alternatives is available in the Appendix A in Annex A. The emulsifiers screened can be divided into 16 different groups based on their chemical composition.

From the groups tested, 9 groups (sorbitan esters, phosphate esters, sugar-based emulsifiers, glycerol esters, polyhydroxystearates, ethyl celluloses, cellulose acetate butyrate (CAB)and polymeric emulsifiers) showed promising results in a first screening with respect to emulsification efficiency or emulsion stabilization. Performance failure on this critical emulsifier function has impact on both end-product quality (deviating particle size distributions and particle defects) as well as production yield. The remaining groups did not fulfil the requirements and were thus not further investigated.

From the groups that successfully passed the first investigational round, 32 promising candidates were found to be potentially viable to replace the most extensively used NPE-containing emulsifiers. From the 32 promising candidates, 14 were chosen to be investigated more thoroughly in a secondary screening. These candidates were selected for this secondary screening based on their chemical structure, previous knowledge, environmental properties and supply aspects. The rejected candidates of the original group of 32 were typically failing with respect to emulsification efficiency and/or insufficient stabilization of emulsion during cooling.

In the secondary screening, the emulsifying conditions were designed to be more demanding on emulsifier function, i.e. more of a stress test was performed. The purpose was to identify emulsifiers with the potential to be implemented in a large part of the product portfolio, i.e. to avoid the scenario of having to implement a number of different emulsifier chemistries in different parts of the product portfolio. A range of concentrations of the 14 emulsifiers were evaluated, and the resulting base matrices were studied by optical microscopy to estimate aggregates and other physical particle defects. Furthermore, the results from particle size distribution measurements, Nuclear Magnetic Resonance (NMR) -diffusion measurements, Fluorescence Polarization Immunoassay (FPIA) and additional microscope studies were also evaluated.

Out of the 14 tested emulsifier candidates, 3 emulsifiers were rejected due to poor initial test. From the resulting group of 11 emulsifiers, 6 emulsifiers were selected for further studies based on the outcome of the test results, and the will to include a number of different emulsifier chemistries.

3.1.1.2 Candidate screening by SP RISE, Technical research institute of Sweden

To generate input from external expertise, and update and extend the list of possible candidates, SP RISE (Technical Research Institute of Sweden) was commissioned in 2016 to perform a desktop study to screen and identify relevant emulsifier candidates. In total, the RISE report suggested 82 candidates. From this report, emulsifiers were structured into six groups which then were included in a program for lab emulsification evaluation. These groups are:

- sorbitan monostearate;

- phosphate ester of ethoxylated oleyl alcohol 3EO;

- phosphate ester of ethoxylated octadecanol 5EO;

- phosphate ester of ethoxylated oleyl alcohol;

- decaglycerol tetraoleate;

- triglycerol diisostearate.

Fourteen of the candidates have a similar structure as the six top candidates identified from the Applicant's initial screening. The remaining candidates were down prioritized in the first screening activity (24) or rejected on the basis of results from previous lab emulsification studies (38).

3.1.1.3 Identification of shortlisted alternatives

In 2017, based on the results obtained from the preliminary alternatives studies, the Applicant compiled a short list of candidates to further investigate the implementation in the manufacture process of the base matrices that have been used as indicator base matrices in development studies. The list of alternatives comprises chemical substances that showed promising results in the preliminary in-house studies (see section 3.1.1.1), the emulsifiers identified by the SP Technical Research Institute and suggestions from suppliers. An overview on the alternative emulsifier identification process is shown in Figure 15.

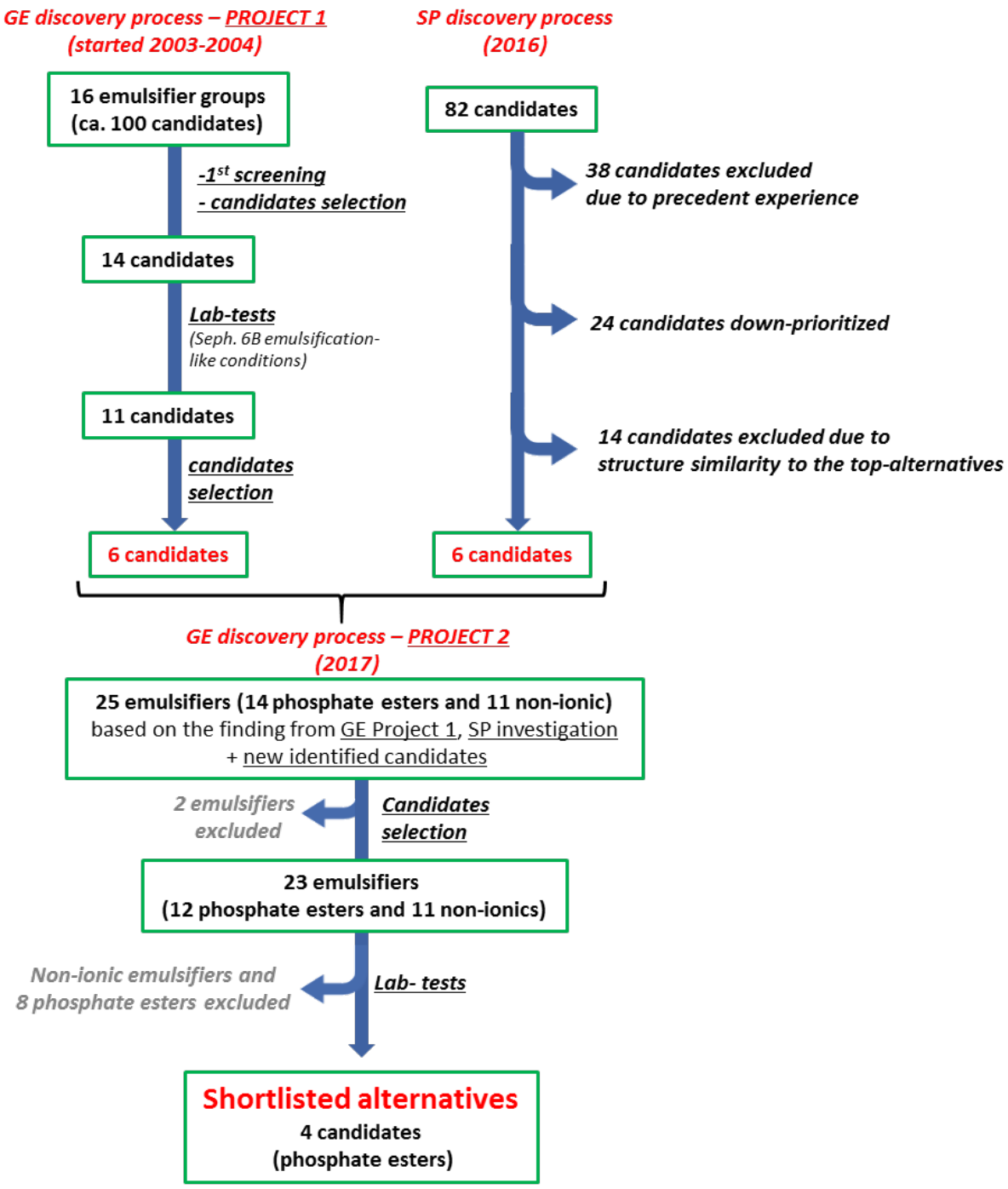


Figure 15: Overview of alternative emulsifiers selection process.

Non-ionic and phosphate esters emulsification candidates were chosen to be tested in an initial screening.

Emulsifier evaluation was conducted in a lab scale by using the emulsification protocol of an indicator base matrix. 25 replacement emulsifier candidates were evaluated with this emulsification protocol. The currently used emulsifier, [redacted] (Emulsifier A), has also been included as reference. Out of those tested, four promising candidates from the

group of phosphate-based esters were identified and are discussed in section 3.3 in the Assessment of Shortlisted Alternatives.

3.1.2 Alternative manufacturing technologies

The NPE-dependent manufacturing technology currently used by the Applicant corresponds to an emulsion templating route for porous polymer particles, and it is considered the only established technology for the manufacturing of this specific type of biopolymer-based chromatography resins; especially for the resins that are based on agarose, which represent the large majority within the product portfolio that use NPE-containing emulsifiers. This has been concluded from historical attempts with development of solvent-free process technologies.

There are a number of synthetic routes available to make porous polymer particles (7). However, the challenging aspect in the present case is that the alternative process technology must lead to end-products that are interchangeable in the user applications, e.g. for biopharmaceutical purification. This implies, among other, that both the surface and the pore space structure of the porous particles need to be replicated in nanometer detail by the new manufacturing technology. With the present emulsion-template technique, both particle surface structure and outer-layer pore space structures are established gradually during the cooling process. The resulting particle surface in this way becomes a template of the emulsion droplet (see Figure 16 for illustration). In this respect the structures formed at the liquid-liquid interface of the emulsion droplet become translated to the corresponding solidified structures of the particle surface. This particle design condition implies that the technical feasibility is very low for the development of an alternative particle manufacturing methods that is not based on emulsion template approaches.

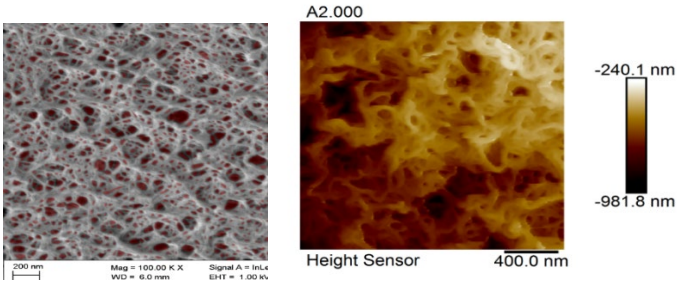


Figure 16: (Left) Scanning electron microscopy of the surface of a dried agarose resin particle, and (Right) atomic force microscopy micrograph of a wet agarose resin particle surface.

3.2 Identification of known alternatives

As a first approach, the Applicant has been assessing the feasibility of replacing NPE containing emulsifiers by an alternative emulsifier using current process conditions (two-phase emulsification process) and reaction conditions (current chemicals, current concentrations, current reaction temperature, etc.). Previously, there have been several R&D efforts to perform a feasibility evaluation of replacing NPE containing emulsifiers in the manufacture of base matrices.

At the present time, there are no known alternatives to replace NPE containing emulsifiers for the manufacture of the base matrices further used in the manufacture of chromatography resin end-products.

The Applicant has performed extensive screening to identify alternative emulsifiers / emulsifier groups that could potentially replace NPE containing emulsifiers in the manufacturing of base matrices using current manufacturing and reaction conditions.

Table 7 summarizes the potential alternatives further considered. These alternatives were categorized according to the test results obtained during the research program described in the previous chapter. For the rejected alternatives, information on observed technical limitations is provided.

Table 7: Potential alternatives taken into account in the assessment

Category	Alternative	Technical limitations
Shortlisted	Phosphate esters	discussed in detail in chapter 3.3.1
Rejected alternatives	Non-ionic Emulsifiers	- increased amount of emulsifier required - performance not robust with regards to stress factors that are part of normal operating conditions -separate study on interfacial tension show that that this group of emulsifiers have significantly lower interfacial activity than phosphate esters - require significant change of buffer system design
	Sorbitan esters	Findings as above for other Non-ionic emulsifiers.
	Sugar based Emulsifiers	- increased amount of emulsifier required - performance not robust with regards to stress factors that are part of normal operating conditions

Category	Alternative	Technical limitations
	Glycerol esters	The glycerol esters showed an overall poor performance, possibly due to the small size of the hydrophilic moiety.
	Oligoglycerol esters	Findings as above for other Non-ionic emulsifiers
	Castor oil ethoxylates	Ethoxylated emulsifiers as a group has shown to not perform well in the present emulsification systems, possibly due to the high solubility of PEO in the emulsion solvent.
	Ethoxylated fatty alcohols	See above.
	PEG-PPG triblock polymers	See above.
	Polyhydroxystearates	Findings very likely in line with observations for other non-ionics and ethoxylated emulsifiers.
	Lecithins	These zwitterionic emulsifiers did not show an overall good function.
	Silicone emulsifiers	General observations overlap with the ones made for Non-ionic emulsifiers
	Ethyl celluloses	The ethyl celluloses were excluded due to previous experiences with very challenging washing processes and residuals.
	Cellulose Acetate Butyrate (CAB)	Emulsifying functions from this polymer were acceptable, but the final cooled emulsion presented deviating properties
	Alkyl aryl sulfonate	Ethoxylated nonionic emulsifier, with a polyethylene glycol chain as the hydrophilic moiety which has been determined as not suitable for this manufacturing application.

Category	Alternative	Technical limitations
	Inorganic particle	As a different category of emulsion stabilizers, inorganic particles were found difficult to use in the screening tests. Some problems with washing after emulsions were also encountered. Since a number of other emulsifiers showed promising results no further work was done to optimize the particle emulsifier systems.

3.3 Assessment of shortlisted alternatives

3.3.1 Alternative 1: NPE-free phosphate ester emulsifiers

The applicant has started to investigate the four most promising candidates that belong to the "Phosphate Ester Emulsifier" group. The strategy is focusing on selecting various phosphate esters with diversified structures, mainly differing in the carbon (C)/ethoxylate (EO) distribution, to investigate the impact of the ratio of hydrophobic/hydrophilic moieties in the structure. The trade name, supplier and the chemical function of the selected candidates for the first screening are presented in Table 8.

Notably, all four shortlisted products are phosphate ester emulsifiers, which correspond to the same chemical design as the presently used NPE containing emulsifiers (see chapter 2.3.3), and importantly to a family of emulsifiers that has a long history of wide spread industrial use, which should enable a robust long-term supply.

A structure of the alternative emulsifier similar to the current NPE containing emulsifiers is expected to require minor changes regarding handling, phase ratio of emulsion design, emulsification energy used (rpm for stirrer and mills), sieving conditions and changes in production equipment and experimental performance. Thus, it is expected that it would most likely lead to less impacts on the base matrix (i.e. porosity, surface structure and dry weight).

Development work is required for process adaptions in both laboratory, pilot, and full manufacturing scales. In addition to process adaptations, design adaptions in terms of buffer compositions and dosage optimization are also required. There are no general adaptations that can be made for all processes for which substitutions are made. Instead, unique solutions must be worked out for every base matrix and process. In general, uncertainties regarding residuals and decomposition patterns, which may influence base matrix quality and emulsifier recycling conditions, affect all alternatives. Further R&D studies need to assess the potential for impacts on base matrix properties.

Table 8: Selected candidates for the first screening.

Trade name	Supplier	Chemical function	C distribution	EO distribution
[redacted] (Alternative Emulsifier A)	[redacted]	C10-16 ethoxylated propoxylated phosphate	12	Not disclosed by supplier
[redacted] (Alternative Emulsifier B)	[redacted]	Polyoxyethylene oleyl ether phosphate	16-18:1	5
[redacted]	[redacted]	Ceteareth-2 Phosphate	16-18	2

Trade name	Supplier	Chemical function	C distribution	EO distribution
(Alternative Emulsifier C)				
[redacted] (Alternative Emulsifier D)	[redacted]	Oleth-3 Phosphate	18:1	3

In order to select the most promising phosphate ester emulsifier groups, a prioritization approach was followed by the Applicant. The criteria used for this exercise were based on the key functionalities of NPE containing emulsifiers described in Chapter 2 "Applied for Use" Scenario and were combined with the technical parameters presented in Table 9. An overview of the prioritization matrix is reported in ANNEX B – Prioritization matrix in the appendix.

Table 9: User Criteria for new emulsifier.

#	User criteria for new emulsifier	Process agent function of emulsifier	Resin product quality impact or malfunction
1	*Chemical stability*	The emulsifier must not decompose during use into components that are non-functional or difficult to remove	Bi-product residues
2	*Easy to analyze*	Emulsifier must be possible to analyze to verify low residue content in final resin product	Bi-product residues
3	*No crosslinking*	Emulsifier chemistry must not interact with cross-linker reaction used in bead porosity formation	Deviating pore size distribution and chemistry
4	*Emulsified bead appearance*	Emulsifier must ensure spherical particle of low defect density	Deviating performance of chromatographic application
5	*Emulsification efficiency*	Emulsifier droplet-reduction function must be compatible with existing process technology	Deviating particle size distribution that may impact properties as flow
6	*Stable beads during cooling*	Emulsifier must prevent droplets to form aggregates during gelation and solidification process	Deviating performance of chromatographic application

#	User criteria for new emulsifier	Process agent function of emulsifier	Resin product quality impact or malfunction
7	*Easy to remove by washing*	Solubility in relevant liquids that can be used in washing protocols	Bi-product residues
8	*Emulsification PSD*	The droplet size formed during emulsification must not deviate strongly from present distribution	Deviating particle size distribution that may impact properties as flow
9	*Process impact of Lot-to-lot variation (emulsifier)*	Process outcome must not show high variability as a function of emulsifier variability	Increased variability of resin properties
10	*Comparable base matrix properties*	The sum of the above properties must result in base matrix properties	Deviating performance of chromatographic application

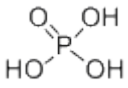
The results of the comparison of the different alternatives show that all candidates are similar. However, [redacted] (Alternative Emulsifier C) is ranked as the top candidate with both [redacted] (Alternative Emulsifier A) and [redacted] (Alternative Emulsifier D) on the second place. [redacted] (Alternative Emulsifier B) has got a lower ranking and has been deprioritized. The emulsifiers "[redacted] (Alternative Emulsifier C)" and "[redacted] (Alternative Emulsifier D)" are both supplied by [redacted]. After further discussions with this supplier about specifications for these two products, the decision was made to prioritize "[redacted] (Alternative Emulsifier D)" over "the related "[redacted] (Alternative Emulsifier C) product". Consequently, [redacted] (Alternative Emulsifier A) and [redacted] (Alternative Emulsifier D) have been prioritized as suitable alternatives and are discussed in depth in sections 3.3.1.1 and 3.3.1.2 , respectively.

3.3.1.1 [redacted] (Alternative Emulsifier A)

3.3.1.1.1 Substance ID and properties

[redacted] (Alternative Emulsifier A) is a clear, yellow and viscous liquid. It was recently launched by the supplier Solvay, with an intended commercial use as a general emulsifier. Furthermore, it also corresponds to the second generation of direct replacement products for the most commonly used NPE containing emulsifier. [redacted] (Alternative Emulsifier A) consists of the components and impurities described in Table 10**.**

Table 10: Substance ID and properties of [redacted] (Alternative Emulsifier A).

Oxirane, 2-methyl-, polymer with oxirane, mono-C10-16-alkyl ethers, phosphates	
Property	**Value**
Molecular structure	N/A
IUPAC name	Phosphate ester of polyoxyalkylated fatty alcohol
EC No.	614-696-4
CAS No.	68649-29-6
Molecular formula	Unspecified
Molecular weight [g/mol]	N/A
Concentration in [redacted] (Alternative Emulsifier A) [%]	>= 80 - < 90
Alcohols ethoxylated propoxylated	
Property	**Value**
Molecular structure	
IUPAC name	1-ethoxydodecane
EC No.	N/A
CAS No.	68213-24-1
Molecular formula	$C_{14}H_{30}O$
Molecular weight [g/mol]	214.39
Concentration in [redacted] (Alternative Emulsifier A) [%]	>= 5 - < 10
Orthophosphoric acid	
Property	**Value**
Molecular structure	
IUPAC name	Phosphoric acid
EC No.	231-633-2
CAS No.	7664-38-2
Molecular formula	H_3O_4P
Molecular weight [g/mol]	98
Concentration in [redacted] (Alternative Emulsifier A) [%]	>= 1 - < 3

3.3.1.1.2 Technical feasibility of [redacted] (Alternative Emulsifier A)

Lab scale process adaptation studies involved manufacturing of resin for indicator product. Several trials have been performed.

Present results indicate that [redacted] (Alternative Emulsifier A) can be implemented using only minor design changes such as using a different buffer concentration. Regarding the process adaptations, only minor modifications appear to be required. Some uncertainties regarding droplet size efficiency as a function of available stirrer rates need to be addressed. Assessment of the resin product quality aspect is limited, since R&D studies have not been able to cover the full scope of this topic so far. However, the following conclusions can be drawn regarding the technical feasibility of this emulsifier:

1. Available data indicate that emulsifier residual levels are acceptable and low.
2. Available data indicate no significant impact on base matrix quality attributes.
3. Uncertainties regarding general resin product impurities remain to be addressed.

[redacted] (Alternative Emulsifier A) may show a bi-product impurity pattern that deviates from the currently used NPE containing emulsifiers. This aspect is currently under evaluation.

3.3.1.1.3 Economic feasibility and economic impacts of [redacted] (Alternative Emulsifier A)

The cost for [redacted] (Alternative Emulsifier A) would be comparable to the NPE containing emulsifier cost. In any respect, the emulsifier cost is a minor part of the entire production costs and is not expected to have significant impact in case of small relative changes. It will be important to establish a supplier agreement for small volume supplies[#5].

3.3.1.1.4 Availability of [redacted] (Alternative Emulsifier A)

While there are a large number (>10) of available phosphate ester emulsifiers from different suppliers, the specific product chemistry of [redacted] (Alternative Emulsifier A) is only available from Solvay. It is expected that the emulsifier is available in sufficient quantities for the Applicant's needs.

3.3.1.1.5 Hazard and risk of [redacted] (Alternative Emulsifier A)

[redacted] (Alternative Emulsifier A) is less hazardous than the emulsifier containing NPE that are currently used in the manufacturing process of the base matrices. Table 11 summarizes the hazard classifications for the phosphate ester [redacted] (Alternative Emulsifier A).

Table 11: Hazard classifications for the phosphate ester emulsifier.

[redacted] *(Alternative Emulsifier A)*			
Class & category	**Hazard statement**	**Hazard statement code**	**Pictogram**
Flammability	N/A	N/A	N/A
Health hazards	Skin irritation 2 H315 Causes skin irritation Eye irritation 2 H319 Causes serious eye irritation	H315, H319	
Source: [redacted] (Alternative Emulsifier A) Safety Data Sheet from [redacted]			

3.3.1.1.6 Conclusions on [redacted] (Alternative Emulsifier A)

Lab scale process adaptation studies (manufacturing of resin for indicator product) have shown that [redacted] (Alternative Emulsifier A) is a promising alternative to the NPE-containing emulsifier currently used in the manufacture of the base matrices. According to available results, only minor process modifications are needed. Further investigations are required to address some minor issues that have been identified during preliminary R&D studies. Moreover, according to the data collected so far, only a preliminary assessment on resin product quality can be made as the full scope of this challenge is yet to be addressed.

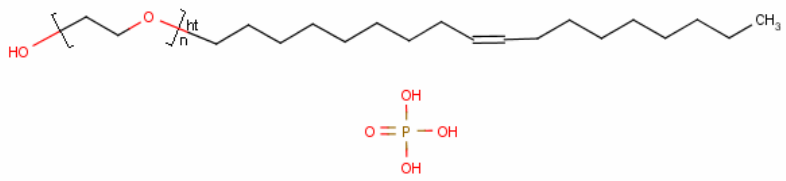
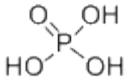
Overall, although [redacted] (Alternative Emulsifier A) showed promising results in the preliminary R&D studies, additional studies are required to assess some criticalities. Therefore, at the current stage, [redacted] (Alternative Emulsifier A) cannot be considered a feasible alternative.

3.3.1.2 [redacted] (Alternative Emulsifier D)

3.3.1.2.1 Substance ID and properties

[redacted] (Alternative Emulsifier D) is a yellow, viscous liquid. It is often used as an emulsifier. [redacted] (Alternative Emulsifier D) consists of the components and impurities shown in Table 12.

Table 12: Composition and properties of [redacted] (Alternative Emulsifier D)

Phosphate ester	
Property	**Value**
Molecular structure	
IUPAC name	Oleyl alcohol, ethoxylate, phosphate
EC No.	933-828-4
CAS No.	39464-69-2
Molecular formula	$(C_{18}H_{36}O).(C_2H_4O)_n.x(H_3PO_4)$
Molecular weight [g/mol]	N/A
Concentration in [redacted] (Alternative Emulsifier D) [%]	>= 50 - <= 100
Orthophosphoric acid	
Property	**Value**
Molecular structure	
IUPAC name	Phosphoric acid
EC No.	231-633-2
CAS No.	7664-38-2
Molecular formula	H_3O_4P
Molecular weight [g/mol]	98
Concentration in [redacted] (Alternative Emulsifier D) [%]	< 5

3.3.1.2.2 Technical feasibility of [redacted] (Alternative Emulsifier D)

Lab scale process adaptation studies involved manufacturing of resin for indicator products. Several trials have been performed including pilot-scale tests.

Present results indicate that [redacted] (Alternative Emulsifier D) can be introduced using only minor design changes. As for the design aspects, only minor process adaptions appear to

be required. Some uncertainties regarding droplet size efficiency as a function of available stirrer rates need to be addressed. Assessment of the resin product quality aspect can only be made very preliminarily in this reporting, since R&D studies have not been able to cover the full scope of this topic so far.

1. Available data indicate that emulsifier residual levels are acceptable and low.
2. Available data indicate no other significant impact on base matrix quality attributes.
3. Uncertainties regarding general resin product impurities are being addressed.

[redacted] (Alternative Emulsifier D) bi-product impurity pattern is expected to deviate from the currently used NPE containing emulsifier given that the NPE containing emulsifier chemistry is replaced by a fatty acid. Otherwise the profile should be overlapping.

3.3.1.2.3 Economic feasibility and economic impacts of [redacted] (Alternative Emulsifier D)

The cost for [redacted] (Alternative Emulsifier D) would be [redacted] compared to the NPE containing emulsifier cost. [redacted]

3.3.1.2.4 Availability of [redacted] (Alternative Emulsifier D)

While there are a large number (>10) of available phosphate ester emulsifiers from different suppliers, the specific product chemistry of [redacted] (Alternative Emulsifier D) is only available from [redacted]. The emulsifier is available in sufficient quantities covering the needs of the Applicant.

3.3.1.2.5 Hazard and risk of [redacted] (Alternative Emulsifier D)

[redacted] (Alternative Emulsifier D) is less hazardous than the emulsifier containing NPE currently used in the manufacturing process of the base matrices. An overview of the risk related to the use of [redacted] (Alternative Emulsifier D) is summarized in Table 13.

Table 13: CLP-classification and labelling for [redacted] (Alternative Emulsifier D).

[redacted] (Alternative Emulsifier D)			
Class & category	***Hazard statement***	***Hazard statement code***	***Pictogram***
Flammability	N/A	N/A	N/A
Health hazards	Skin irritation 2 H315 Causes skin irritation Serious eye damage 1 H318 Causes serious eye damage	H315, H318	
Source: [redacted] (Alternative Emulsifier D) Safety Data Sheet from [redacted]			

3.3.1.2.6 Conclusions on [redacted] (Alternative Emulsifier D)

Lab scale process adaptation studies (manufacturing of base matrices for indicator products) have revealed that [redacted] (Alternative Emulsifier D) is a promising alternative to the NPE-containing emulsifier currently used in the manufacture of the base matrices. According to the available results, only minor process modifications are needed. Further investigations are required to address some issues that were identified during preliminary R&D studies. Moreover, according to the available data, only a preliminary assessment on resin product quality can be made as the full scope has not yet been covered.

Overall, although [redacted] (Alternative Emulsifier D) showed promising results in the preliminary R&D studies, additional studies are required to assess some remaining uncertainties. Therefore, at the current stage, [redacted] (Alternative Emulsifier D) cannot be considered a feasible alternative.

3.4 Outlook: Current R&D project

In order to further assess the technical feasibility of alternative emulsifiers in the manufacture of polysaccharide-based porous particles, the Applicant will need to perform an R&D and manufacturing program looking at adaptation of the current process and reaction conditions needed for the use of an alternative emulsifier.

Since 2003, the Applicant is engaged in finding a suitable alternative to NPE containing emulsifiers for the manufacture of base matrices. As reported in Table 14, several R&D phases, including the identification of alternatives, the increase of lab-scale manufacturing capability and the development of robustness tests, were successfully completed in the last years. R&D efforts are currently focusing on investigating the impact of the identified alternative(s) on resin product quality and on pilot-scale tests for the short-listed alternatives. An implementation plan for new process equipment (reactor, stirrers, etc.) is also on track. The next R&D steps include the optimization of the production method design for the alternative, technical trials, validation plans, and the submission of documentation required for customer notification. The Applicant believes that the R&D phase for the first (of 13 groups in total) product group will be completed in 2021.

A preliminary R&D and manufacturing program plan has been prepared and covers all the activities that the Applicant will perform for all product groups. The R&D activities that have been completed prior to and during the assessment of shortlisted alternatives and the status of each activity are shown in Table 14.

Table 14: Summary of R&D activities for NPE substitution.

#	R&D activity	Scope	Result	Status
1	*Historical development project on NPE-replacement*	Screen, identify and implement emulsifiers to replace currently used NPE-containing substances	Activity put on-hold 2004 due to limited progress	**Completed**
2	*CRO project on alternative generation*	External research partner employed to create emulsifier candidate list	A large number of emulsifier groups and specific products identified as candidates.	**Completed**
3	*Desktop prioritization*	A 1st alternative list created based on the analysis of CRO report versus historical project results	About 25 alternatives selected for lab-scale evaluation	**Completed**
4	*Establish high capacity lab-scale manufacturing facilities*	Increase lab-scale manufacturing capability adapted for emulsifier evaluation	A novel lab station comprising four parallel units established.	**Completed**
5	*Lab-scale screening 1st alternative list*	Lab-scale emulsification and production of one resin prototype	Down-selection to short-list of about 5-7 alternatives	**Completed**
6	*QbD (Quality by Design) study on product quality impacts*	Study of the design conditions under which emulsifiers impact intrinsic resin product properties	Preliminary results have outlined a relevant design window for phosphate ester emulsifiers	**Ongoing**
7	*Analytical method development*	Analytical methods that enable determination of NPE and emulsifier residues in product and process streams.	Methods are underway to be validated for NPE and emulsifier residue level determination.	**Ongoing**
8	*Baseline development for residue for resin products and process streams*	Baseline levels for a selected number of existing emulsifiers and production methods.	TBD	**Not started**
9	*Robustness tests and prioritization matrix evaluation*	Alternative assessment studies of four candidates – technical feasibility, economic feasibility and availability.	Three alternative emulsifier products concluded and prioritized.	**Completed**
10	*Pilot-scale tests of prioritized alternatives.*	Small number of pilot scale manufacturing trials	Outcome of pilot-scale tests confirm promising technical feasibility of chosen alternatives	**Ongoing**

#	R&D activity	Scope	Result	Status
11	*Implementation plan for new process equipment: reactor, stirrer, etc.*	Improved production equipment will be introduced in tandem with emulsifier change	New efficient production equipment will reduce consumption of solvents and emulsifiers.	**Ongoing**
12	*Verification plan development for 1st group of resin products*	Plan to cover all the R&D activities needed for verification of process conformance and product equivalence	TBD	**Not started**
13	*Technical trials and verification*	Generate the results that correspond to underpinning data required for a decision to start validation of new emulsifier and production process.	TBD	**Not started**
14	*Validation plan for 1st group of resin products*	Show manufacturability for all concerned resins using the new emulsifiers	TBD	**Not started**
15	*Validation for 1st group of resin products*	Data that demonstrate manufacturability	TBD	**Not started**
16	*Development, verification and validation of remaining resin product groups*	TBD	TBD	**Not started**
17	*Submit documentation for customer change notification process*	Customers subscribing to change control notification for related product to be informed about emulsifier change.	TBD	**Not started**

Staggered replacement approach

The different base matrix resins described in this AoA have been classified into various product families (see chapter 2.1). Each family was then assigned to a certain priority level based on the volume of NPE-containing emulsifiers used for their manufacture. Base matrix families whose manufacturing requires a larger volume of NPE containing emulsifiers, and, therefore, of NPE, were given the highest priority level, and those using the lower amount of NPE containing emulsifiers were given the lowest priority. To substitute these NPE containing emulsifiers in the manufacturing process of base matrices, the Applicant aims at following a staggered approach, starting with the base matrix families assigned to the highest priority levels and sequentially substituting product families with lower priorities. The use of NPE containing emulsifiers will therefore be substantially reduced during the first years of the full substitution program.

This staggered approach is justifiable firstly from an economic perspective because laboratory investigations are complex and require considerable investment in term of resources and time, and secondly from a technical perspective because it would not be feasible for the Applicant to

implement an alternative emulsifier in the manufacture process of all products in parallel due to limited access to manufacturing equipment since the Applicant needs to use this equipment for the manufacture of other base matrices and for the manufacture of the base matrices using NPE containing emulsifiers due to market demand. Furthermore, the staggered approach is critical in terms of risk mitigation, as R&D processes include an inherent uncertainty. What works for one base matrix family does not necessarily work for another because the various product families are different on the microlevel. Issues that will be identified during the staggered approach will allow the Applicant to focus on the specific impacted product families and building up on the knowledge acquired as substitution progresses, whereas if a parallel approach was followed, new candidates would need to be evaluated from start for all product families if failures arise.

Tasks and timelines for each product families

The Applicant will replace 13 different product families. The tasks outlined in Table 14 and that must be carried out for substituting NPE-containing emulsifiers, as well as their approximate duration are shown in Figure 17. The tasks in blue must be carried out for each product families. The main tasks that must be completed for successful substitution of the NPE-containing emulsifiers are: development of characterization methods and a product base line (approximately 3 years), development of production base methods (6 to 8 months), installation of reactors and product verification (9 months), technical trials and process verification (9 months), process and design validation (9 months), and notification of changes to clients (9 to 12 months, please see more details below).

Please note that the activities for the substitution of NPE containing emulsifier used for the manufacture of the first product family (green bars in Figure 17) are currently under investigation. Initial general substitution activities are currently carried out which in best case (meaning the alternative identified for the first product family is applicable to all other product families as well) will not be needed for all remaining product families. Once the feasibility and development studies for the first product family are completed, the Applicant will start the staggered substitution process for the remaining product families.

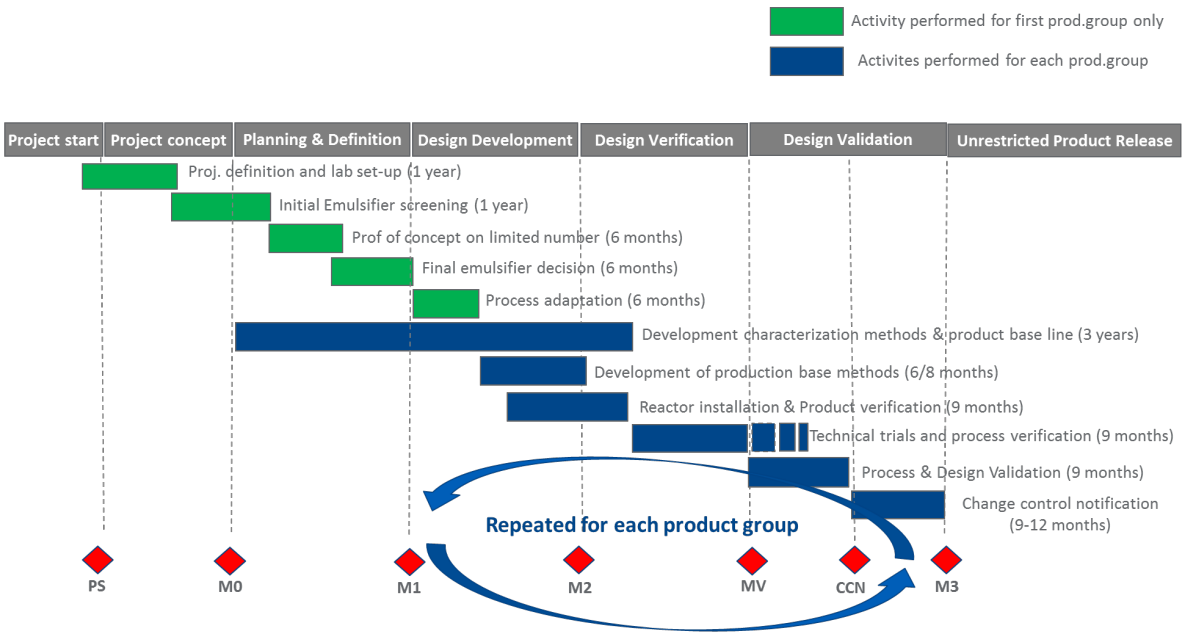


Figure 17. Substitution activities performed per product family. The activities in green only need to be carried out for the first product family. The activities in blue need to be performed for all remaining product families.

As shown in Figure 17, the tasks for substitution are mostly carried out in a sequential order. This is because complete substitution requires the progressive development and implementation of the alternative until a fully developed process can be established (most of the tasks require the output from the previous one). Some tasks, however, can be carried out in parallel, such as the development of production base methods and manufacturing equipment installation. Most importantly, technical trials and process verification can only be started once the manufacturing equipment has been installed, the development of characterization methods and product base line have been concluded and required data on process and design validation are obtained from the technical trials and process verification. These steps are potentially iterative in the sense that if a potential alternative is found to be unfeasible, the whole process must be started again from the development of characterization methods and product base line.

Customer notification

The final step in the substitution process is the change control notification (CCN) sent to customers. GEHC LS customers, including biopharmaceutical companies, academia and the food industry, use the Applicant's chromatography resins in highly technical and sensitive applications and often in regulated laboratory and industrial settings (see chapter 2.3.1). Customers will be notified about all changes made in the manufacture of the chromatography resins, as the replacement of the emulsifiers containing NPE constitute a major change. Customers need to be aware of any change that might alter the properties or performance of a material used in manufacturing or testing their end-products, or which will impact manufacturing-related documentation. These changes need to be known prior to full manufacturing implementation by the Applicant so that customers can fully evaluate the

changes and have time to plan for and qualify the changes. Customers may have varying requirements for what needs to be included in customer notifications. For medical applications, the efficacy, quality and safety of the final product manufactured by the customer needs to be ensured. Therefore, companies manufacturing and marketing these products must follow Good Manufacturing Practices (GMP) and operate within a highly regulated environment. GMP for biological API's requires extensive studies to validate that the materials, equipment, and processes used for manufacturing of these API's consistently deliver products that meet specifications upon release and throughout their labeled shelf life. A change in their end-product formulation may force customers to revalidate material, GMP practices, and submit regulatory registrations in various geographies. Depending on the customer specific application, this process could take several years.

Substitution timeline for all product families

The staggered substitution approach is displayed in Figure 18. After the development phase for one product family is successfully passed and the validation phase starts, the development phase of the next product family can be initiated. The substitution timeline shown in Figure 18 was developed considering all product families and the approximate time that each product family would be needed for substitution. As the aim is to implement the same alternative in the production process of all product families, so that the initial activities carried out for the first product family do not need to be repeated. However, it is unclear at this time whether substitution can be carried out for all product families with the same emulsifier alternative. Moreover, additional time might be required by customers to evaluate these changes. Therefore the 12 years review period applied for only includes the time that the Applicant needs for substituting the emulsifiers containing NPE in its manufacturing processes.

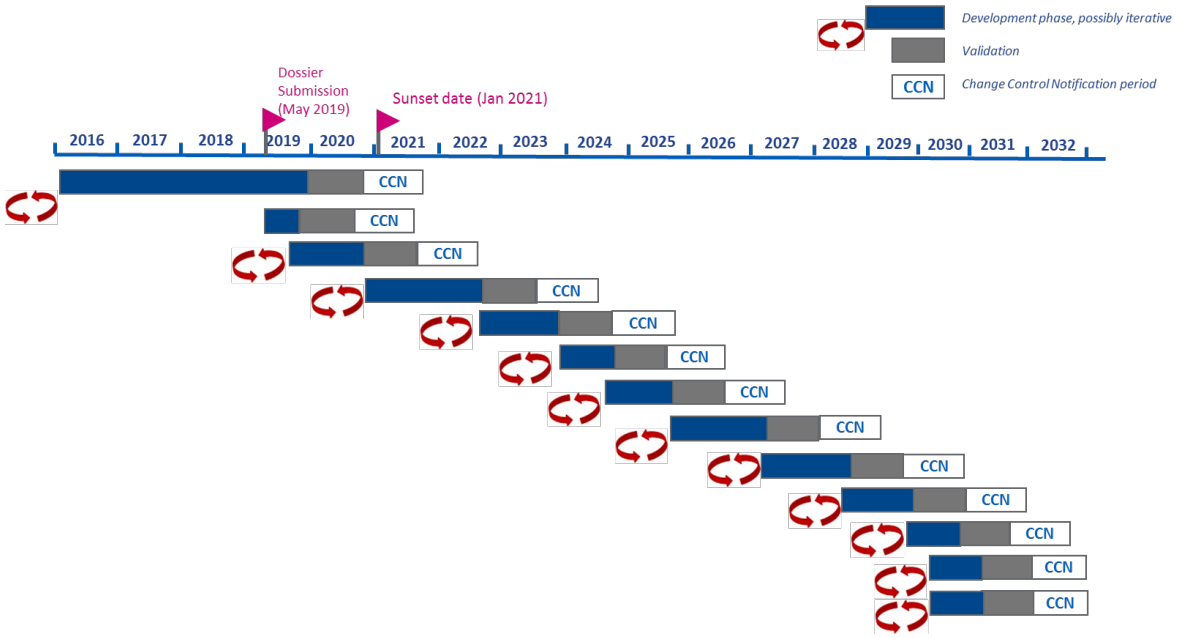


Figure 18: Staggered substitution approach.

After identification of alternatives, substitution efforts for the first product family started in 2015. Please note that failures can occur at any time during the R&D process (development, validation phase) for the different families. In that case, R&D for that family would need to start from an early development phase again. The length of the development phase is varying for the different families as learnings from previous families can be applied and the number of products per family is different.

The Applicant has the ambition to gradually reduce the NPE containing emulsifier usage over the review period applied for (12 years). However, as the feasibility understanding of the candidates is not completed yet, there is an inherent uncertainty on the substitution plan. Therefore, the timeline shown in Figure 18 could vary significantly depending on the results observed throughout the substitution process.

In summary, using a best-case approach, the Applicant applies for a review period of at least 12 years in order to successfully implement the substitution of all emulsifiers containing NPE used in the manufacture process of base matrices in scope of this AfA.

3.5 The most likely non-use scenario (NUS)

The Applicant has considered different scenarios in case authorisation for the continued use of NPE containing emulsifiers should not be granted. A detailed assessment of these different scenarios resulted in one most realistic NUS.

The following scenarios have initially been considered for assessment:

1) Substitution of NPE containing emulsifiers by implementing a different industrial process and/or an alternative emulsifier
2) Permanent shutdown of the manufacturing of NPE-dependent chromatography resins at the Uppsala site with relocation of the manufacturing processes to a non-EEA country
3) Permanent shutdown of the manufacturing of NPE-dependent chromatography resins without relocation to a non-EEA country, i.e. discontinuation of the end-products
4) Temporary shutdown of the manufacturing of NPE-dependent chromatography resins at the Uppsala site until an alternative is developed and implemented.

The following chapters describe the scenarios in more detail.

3.5.1 Scenario 1: Substitution of NPE containing emulsifiers by implementing a different industrial process and/or an alternative emulsifier

This scenario considers the replacement of NPE containing emulsifiers by a different emulsifier which could provide the same performance to the end-products and/or a different manufacturing process which would not require the use of NPE containing emulsifiers or any other emulsifiers.

As it can be seen from the results of the AoA, no alternative emulsifier or industrial process which could provide the end-products with the same properties as in the applied for use scenario are readily available at the time of the preparation of this AfA. Therefore, this scenario has been discarded and its likelihood will not be assessed in Section 3.5.5.

3.5.2 Scenario 2: Permanent shutdown of the manufacturing of NPE-dependent chromatography resins at the Uppsala site with relocation of the manufacturing processes to a non-EEA country

This scenario involves the shutdown of the NPE-dependent chromatography resins manufacturing at the Uppsala site and the subsequent relocation of the manufacturing to a non-EEA country. The site in Uppsala would continue operating only with the production lines not related to the use of NPE containing emulsifiers. In this case, the production of NPE-dependent chromatography resins in Uppsala would be operative until the sunset date. Afterwards, the relocation of the manufacturing processes of the affected end-products would start which is estimated to take around 10 to 12 years until the new facility in a non-EEA country could be fully operational. Thus, supply disruptions for GEHC LS customers during the relocation process would occur. The period of 10 to 12 years has been calculated based on the assumption that the time for setting up a new manufacturing site for end-products manufactured with NPE containing emulsifiers is estimated to about 7 years from start of technical design to full operational implementation, depending on where the site would be located. Time for construction of the manufacturing plant is estimated at 5 years. Time for obtaining operation permits and setting up the operation infrastructure will most probably vary depending on country and region. When the construction of the plant is finalized, process validation can be initiated, which is estimated to about 5 years (including Change Control Notification periods for all end-products).

In terms of investment, a calculation has been done for the NPE related end-products. The total cost estimation is as follows:

- **Facilities:** [redacted]. This cost includes costs for construction of the production plant, storage buildings, laboratories for quality control, offices and landmark.
- **Process equipment and installations:** [redacted]. This cost includes costs for reaction vessels & process equipment, piping, electric & instrumentation, automation and other equipment.
- **Infrastructure :** [redacted]. This cost includes costs for construction of tank farm for e.g. solvents, solvent recovery plant, water supply, pressurized air and nitrogen supply, WWTP, electricity supply, sprinklers and other security needs.
- **Overhead**: [redacted]. This cost includes costs for project and installation, design, commissioning and qualification.
- **Contingency (40%):** [redacted]

- **Total:** [redacted][3]

Since it would not be possible to build any significant stocks at the Uppsala site to supply customers during the relocation time, a supply interruption during the entire relocation period is expected in this NUS. This supply interruption would impact not only the Applicant's business in Uppsala, but also customers such as the biopharmaceutical industry, the food sector and academia. In the case of the biopharmaceutical industry, a supply interruption of NPE-dependent chromatography resins would have extreme consequences on the availability of some biological API's manufactured using these chromatography resins, and consequently impacts millions of patients/consumers worldwide. Moreover, since the Applicant would not be able to fulfil customers' demands and requirements set in supply contracts, the Applicant would have to face multimillion Euro claims in terms of commercial penalties as well as tremendous negative publicity and loss of reputation for GE, GEHC and GEHC LS.

Employees currently working in the chromatography resins facility in Uppsala would have to be dismissed (or at least a significant part of them).

The likelihood of this scenario in comparison to other scenarios which have not been directly rejected is assessed in Section 3.5.5.

3.5.3 Scenario 3: Permanent shutdown of the manufacturing of NPE-dependent chromatography resins without relocation to a non-EEA country

In this scenario, the Applicant would shut down the production lines at the Uppsala site which are currently manufacturing NPE-dependent chromatography resins and no relocation would occur. The site in Uppsala would continue operating only with the production lines not related to the use of NPE-dependent chromatography resins.

Similar to what was described for the scenario 2, a permanent shutdown of the NPE-dependent chromatography resins production (without relocation) would result not only in massive financial impacts to the Applicant, but also in long-term impacts to the biopharmaceutical industry and its patients, and the food sector. Significant commercial penalties and loss of reputation can also be foreseen as impacts for the Applicant.

Given the reasons mentioned above and the fact that a permanent shutdown of the NPE-dependent chromatography resins production (without relocation) would be related to long-term impacts to the entire biopharmaceutical industry and its patients, and the food sector, the termination of NPE-dependent chromatography resins manufacture is not an alternative and the Applicant is committed to continue providing these end-products to its customers (8) . This scenario has, therefore, been directly rejected and its likelihood will not be assessed in Section 3.5.5.

[3] Calculated with an exchange rate of EUR 1 = USD 1.1609 (as of September 3rd, 2018).

3.5.4 Scenario 4: Temporary shutdown of the manufacturing of NPE-dependent chromatography resins at the Uppsala site until an alternative is developed and implemented

In this scenario the Applicant would stop the manufacturing of NPE-dependent chromatography resins in Uppsala at sunset date until an alternative to NPE containing emulsifiers (new emulsifier(s) or new technology(ies)) could be implemented. This is expected to take at least 12 years. In order to develop and implement an alternative to NPE containing emulsifiers in the production of affected chromatography resins, the Applicant would incur in significant R&D costs. Other production lines at the site in Uppsala (which are not related to the use of NPE containing emulsifiers) would continue operating normally.

The estimated cost for the R&D and manufacturing program is [redacted][4]). The main contributions to this cost are the manning costs required for the R&D and manufacturing work ([redacted]), the cost for technical trials and verification batches in production scale ([redacted]) and necessary Capital Expenditure (CAPEX) investments for re-designing existing manufacturing equipment ([redacted]). The CAPEX investments include costs for laboratory equipment and a new manufacturing reactors. It is important to note that the cost of the R&D and manufacturing program might increase if the technical results show that several alternative emulsifiers must be evaluated to finally obtain a technically feasible alternative.

This cost has been determined for the emulsifiers presented in the assessment of shortlisted alternatives and therefore might be re-assessed once an alternative emulsifier is chosen and is technically feasible.

The Applicant would not be able to build any significant stocks to supply its customers during the temporary shutdown period, leading therefore to a supply interruption during the entire temporary shutdown period of the affected production lines (manufacturing NPE-dependent chromatography resins).

In conclusion, this scenario would lead to a temporary disruption in the supply of more than 120 different chromatography resins to GEHC LS' customers after the sunset date and during the development and final implementation of an alternative. Similar to what was described for the scenario 2, a supply interruption would result not only in massive financial impacts on the Applicant, but also in impacts to the biopharmaceutical industry and its patients, and the food sector. Significant commercial penalties and loss of reputation can also be foreseen as impacts on the Applicant.

[4] Calculated with an exchange rate of EUR 1 = USD 1.1609 (as of September 3rd, 2018).

The likelihood of this scenario in comparison to other scenarios which have not been directly rejected is assessed in Section 3.5.5.

3.5.5 Likelihood of the presented scenarios and definition of the most realistic NUS

The likelihood of the scenarios described above is assessed in detail in this section. As stated, scenario 1 is excluded from the analysis due to the non-availability of alternative emulsifiers or alternative processes. Scenario 3 is also excluded because of its high permanent (or at least long-term) impact in the supply chain.

This likelihood analysis is therefore constrained to scenarios 2 and 4 and is performed qualitatively (see Table 15).

Table 15: Comparison of costs between scenarios 2 and 4.

Impacts	Scenario 2: permanent shutdown of the manufacturing of NPE-dependent chromatography resins with relocation to a non-EEA country	Scenario 4: temporary shutdown of the manufacturing of NPE-dependent chromatography resins until an alternative is developed and implemented
Costs of decommissioning installations	Medium	Low
Investments in R&D and/or in the relocation production facility	High	Medium
Disruption of supply	High	High
Expenses with customer requalification	Medium	Medium
Inventory costs	Low	Low
Transport costs	Low	None

As it is shown in the qualitative assessment, **scenario 4 would be the most likely NUS** as it would lead to lower costs than scenario 2. In the case of scenario 2, it would incur the Applicant with high investments related to the relocation itself such as building new installations outside the EEA, while other impacts would be equal or higher than for scenario 4. Furthermore, since regulatory demands are increasing globally and a ban on NPE could take place in several jurisdictions, relocation of the manufacturing processes to a non-EEA country (NUS 2) is not seen as a long-term and sustainable solution.

Despite the fact that in the most likely scenario (NUS 4) there would be investments in R&D (to develop and implement an alternative to emulsifiers containing NPE), such R&D investments are estimated to be lower than the investments needed for the relocation of the manufacturing processes in a non-EEA country (NUS 2).

4 IMPACTS OF NOT GRANTING AUTHORISATION

The impacts assessed in this chapter are based on the comparison of the baseline (summarized in Section 2) versus the NUS 4 (most-realistic scenario, summarized in Section 3.5.5). Figure 19 and Figure 20 present the supply chain for the baseline scenario and the NUS, respectively. As shown, in the case of a non-granted authorisation, the supply chain would be highly affected.

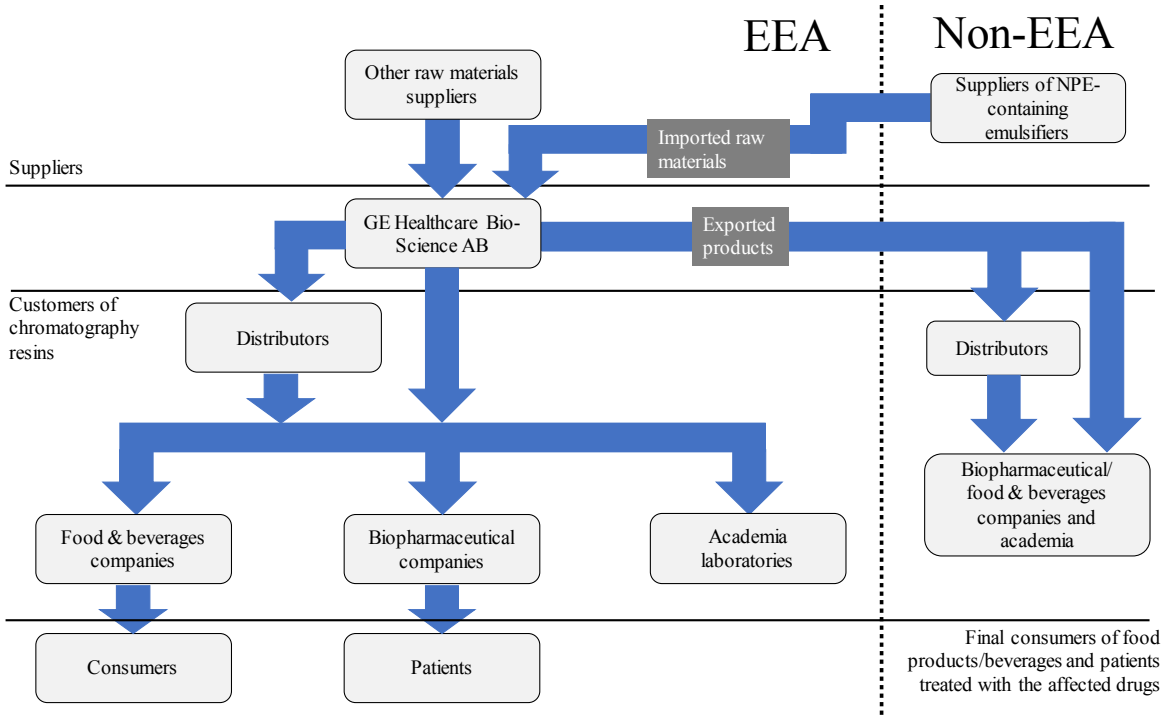


Figure 19: Supply chain in the baseline scenario.

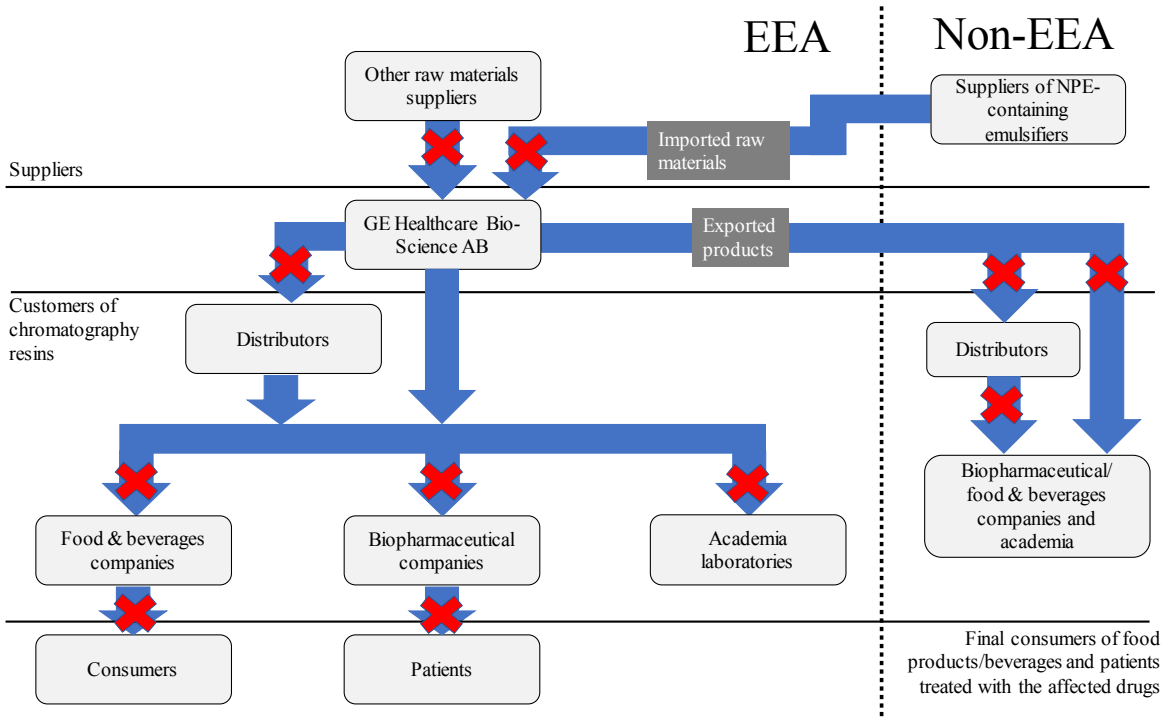


Figure 20: Summary of changes to supply chain in the NUS until an NPE alternative can be developed and implemented.

4.1 Supply chain disruption

In the most-realistic NUS (NUS 4) there would be a supply chain disruption that would impact the applicant, its customers (biopharmaceutical manufacturers) and patients/public. The impact of the most-realistic non-use scenario (NUS 4) on patients depending on medicines is by far the most severe impact of all presented impacts along the supply chain.

Impact on biopharmaceutical manufacturers (customers purchasing chromatography resins)

There would be a disruption in the supply of more than 120 different chromatography resins to the biopharmaceutical industry after the Sunset date and during the implementation of an alternative, having extreme consequences on the availability of some biological APIs manufactured using these products. Figure 21 shows the use of chromatography resins in pharmaceutical production.

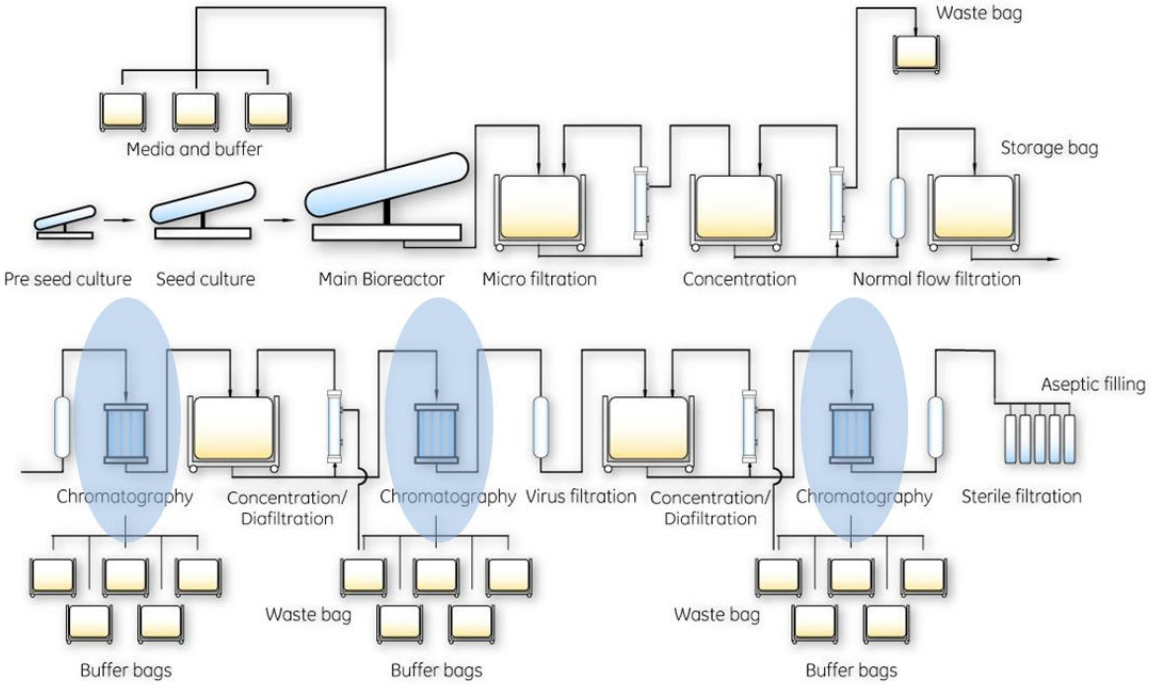


Figure 21: Example of generic flow scheme for the manufacturing of biopharmaceuticals with highlighted area (blue) for chromatography applications.

About 40 % of the biopharmaceutical companies using GEHC LS chromatography resins in approved and registered manufacturing processes for human therapeutics and vaccines are in the EEA. In total, more than 70 biopharmaceutical companies having approved and registered manufacturing processes of biological APIs using the affected chromatography resins would be impacted in the most-likely non-use scenario (NUS 4). In this NUS, the biopharmaceutical customers using these products would possibly have three alternative options:

1) To discontinue the biological APIs, and thus the medicines, that are manufactured with the affected chromatography resins supplied by GEHC LS. These products are used in at least 190 manufacturing processes of approved and registered biological APIs.

2) To suspend the manufacture of the biological APIs manufactured with GEHC LS's affected chromatography resins until these products are available again after successful implementation of an alternative by the Applicant (after a disruption of at least 12 years). This would mean that these customers would not be able to manufacture the registered and approved APIs during a period of 12 years.

3) To completely redesign the manufacturing processes of the biological APIs which currently make use of GEHC LS's affected chromatography resins in one or several of their manufacturing steps. Since the one to one replacement of these products by alternative products is not possible due to the specificity of these products and the

non-availability of these products or equivalent products from other suppliers, the biopharmaceutical customers would try to develop manufacturing processes without these products. As shown inFigure 21, manufacturing processes of biological APIs are complex processes made of several steps, such as filtration and chromatography steps, which are interconnected. Any changes in one of the steps of these manufacturing processes would most likely result in the need to change or adapt some of the other steps, if not whole manufacturing process. Redesigning the whole manufacturing processes of the impacted biological APIs would mean:

- **Additional costs derived from:**
  - The development of a new manufacturing process
  - Performing extensive and lengthy comparability studies to secure that the APIs obtained from the new manufacturing process have similar characteristics than the current APIs obtained with NPE-dependent chromatography resins (e.g. bioassays and/or pharmacokinetic /pharmacodynamic studies and animal testing). The estimated total time for assessing, testing and implementing these new manufacturing processes would be up to 12 years for each biopharmaceutical end-product.
  - Refiling approved market authorisation by the regulatory authorities, due to change in manufacturing process of the biological API would also be required. Re-registration and re-approval of the manufacturing process by US FDA and EMA or other similar authorities in other jurisdictions are time-consuming and expensive processes and can take up to 2 years.
- **In the worst-case scenario, i.e. refiling is not approved it might result in lack of availability of life-sustaining or life-enhancing biopharmaceuticals for an indefinite period.**

Even if new manufacturing processes for the impacted APIs could be developed and implemented, it would require several years before the biopharmaceutical customers can place again on the market the medicines formulated from the impacted APIs.

All described options would result in very high economic impacts on the customers in terms of revenue losses (more than EUR 130 billion per year), penalties (since they would not be able to fulfil their contracts) and reputation. It is difficult to assess all the impacts that any of these three options would have on the biopharmaceutical customers, but they are judged to be extremely severe. This situation would inevitably lead to a shortage of medicines for treatment of certain lethal or debilitating diseases during at least 12 years.

Impacts on public/patients

If GEHC LS's chromatography resins, in scope of this AfA, are not available to biopharmaceutical customers having approved and registered manufacturing processes of biological APIs using these products, at least 190 human therapeutics and vaccines would not be available on the global market. These human therapeutics and vaccines cover widespread therapeutic areas such as: diabetes, anaemia, haemophilia, blood coagulation factors, rheumatoid arthritis, psoriatic arthritis, growth hormone deficiency, fertility, leukaemia, hepatitis, ulcerative colitis, psoriasis, thrombocytopenia, myocardial infarctions, HAE attacks, meningitis, neuroblastoma, myocardial infarctions, influenza, immunosuppressive treatment before transplantation, wet AMD and various rare diseases. The human therapeutics and vaccines are intended for treatment of millions of patients all over the world with serious, possibly life-threatening diseases. Cessation of supply of the GEHC LS's chromatography resins in scope of this AfA to the biopharmaceutical industry during the 12-year period necessary for these products to be available again will result in a serious threat to human health for an extremely large population.

Some of these human therapeutics and vaccines might be available from other biopharmaceutical companies not using GEHC LS's affected chromatography resins in any of the steps of their manufacturing processes of these biological APIs and medicines. Nevertheless, the most-realistic non-use scenario (NUS 4) would still create a shortage in availability of some of these medicines, such as insulin, and in a worst-case scenario, some of these medicines would not be available any longer for the treatment of millions of patients with serious, possibly life-threatening diseases.

Impact of the supply disruption on the Applicant

Since the Applicant would not be able to fulfil customers' demands and requirements on NPE-dependent chromatography resins, this would lead to:

1) Claims of multimillion Euro amounts in terms of commercial penalties. This would also imply a loss of reputation and market as customers would turn to competitors when developing new manufacturing processes of human therapeutics and vaccines. In a worst-case scenario, this situation could seriously compromise the long-term viability of GEHC LS operations, especially at the Uppsala site, resulting in additional job losses in the EEA (and outside the EEA) and profit losses globally.

2) Since GEHC LS provides start to finish technical solutions for all steps of the manufacturing process of biopharmaceuticals and other products from its portfolio including the NPE-dependent chromatography resins, the non-availability of NPE-dependent chromatography resins during a 12-year period would consequently lead to a decreased need of other GEHC LS products. In addition, GEHC LS competitors would also be affected as their products are also used together with GEHC LS NPE-dependent chromatography resins by some biopharmaceutical customers. It is difficult

to monetize this impact since the Applicant does not have full insight in the full manufacturing processes of its customers using the NPE-dependent chromatography resins and other products in its portfolio.

4.2 Social impacts

Due to the temporary shutdown of NPE-dependent chromatography resins production, approximately between [redacted] employees will be dismissed in EEA. Those dismissals comprise all [redacted] workers currently involved in the manufacture of NPE-dependent chromatography resins and other workers (approximately [redacted]) which would be indirectly impacted due to the relevance of the chromatography resins business for the financial sustainability of the whole Uppsala site. Considering this, the social costs related to expected job losses in the most realistic NUS (NUS 4) have been calculated assuming a "worst case scenario" and a "best case scenario". In the "worst case scenario" it is assumed [redacted] employees will be dismissed and in the "best case scenario" has been estimated to [redacted] dismissals.

Following the methodology presented in a report commissioned by ECHA (9) the social costs related to expected job losses in NUS 4 are valued considering the following components:

- The value of lost output/wages during the period of unemployment
- The cost of searching for a new job
- Recruitment costs
- The ´scarring costs´ (i.e. the impact of being made unemployed on future earnings and employment possibilities)
- The value of leisure time during the period of unemployment

The latter component is seen as a negative cost (i.e. a benefit) of unemployment. As such it is subtracted from the total cost resulting from the first four components.

The figures from the aforementioned paper have been updated to 2016 levels by using the wages as updated in the paper from Rogers and Philippe (10) and the proportions for duration of unemployment in 2016 as of Eurostat (11).

Table 16 and Table 17 summarize the monetised social costs of [redacted] dismissals respectively.

Table 16: Monetised "worst-case" social cost of dismissals at GEHC LS businesses in the NUS.

Number of dismissals	[redacted]
Unemployment social cost of one job position in Sweden (2016 value)	EUR 95,357
Unemployment social cost of one job position in Sweden adjusted to 2021 values (using Eurostat's 2007-2016 average inflation rate of 3.4 %) (12)	EUR 112,708
Social cost due to dismissal of GEHC LS workers	[redacted]

Table 17: Monetised "best-case" social cost of dismissals at GEHC LS businesses in the NUS.

Number of dismissals	[redacted]
Unemployment social cost of one job position in Sweden (2016 value)	EUR 95,357
Unemployment social cost of one job position in Sweden adjusted to 2021 values (using Eurostat's 2007-2016 average inflation rate of 3.4 %) (12)	EUR 112,708
Social cost due to dismissal of GEHC LS workers	[redacted]

The Uppsala Region: qualitative assessment about unemployment

Uppsala is the fourth biggest city in Sweden and has around 150,000 inhabitants. The city is located about 70 km North of Stockholm. Although Sweden's economy relies heavily on foreign trade with timber, hydropower and iron, the economy of Uppsala is academia oriented, especially medical research is very important. Therefore, major life science companies have chosen to have bases in or around Uppsala. (13)

The county of Uppsala has a well-educated population; a high proportion of inhabitants has tertiary education. Compared to the countries average the proportion of the population with an education level lower than secondary education is smaller. Most employees work in the health care / life sciences and social work sectors or in sales, hotels and restaurants (14).

The unemployment rate in the county of Uppsala is about 6% of the working population. (14)

GEHC Biosciences AB is the largest private employer in the county of Uppsala and its activities contribute to the growth of the Uppsala region and in particular to the biotechnology and life sciences sectors. The region of Uppsala hosts more than one hundred companies in the life science sector encompassing activities in the biotech, pharmaceutical, biopharmaceutical, MedTech and diagnostic industries. These companies range from large multinationals via small

and medium sized enterprises to small start-ups. The companies have R&D facilities, production facilities and perform marketing & sales tasks. Marketing & sales is very important as the industry exports 95% of its products. The Uppsala region increasingly gains expertise in foreign markets and establishes important networks.

The life science sector in and around Uppsala employs 5,000 employees. Five large multinational companies in the region employ 70% of all employees in this sector. The biggest of them is GEHC Bio-Sciences AB followed by Fresenius Kabi (15)**.**

Although the region of Uppsala has potential employment opportunities for qualified workers that have to be dismissed by GEHC Bio-Sciences AB in the most-realistic NUS (NUS 4), it is important to note that the Applicant is the biggest private employer in the region. Moreover, all employees will have to be dismissed at the same time and it is very unlikely that all employees will immediately be able to find a job with one of the other companies in that sector. Even if some of these workers could move abroad and work for competitors, willingness to move abroad is certainly low for most of workers involved in manufacture. As explained in this section, the companies in Uppsala that are active in the life science sector are operating in different industries. Therefore, employees previously working for the Applicant that have to be dismissed may need additional training to become qualified for the jobs offered by other companies in the life science sector in the region.

4.3 Economic impacts: loss of profits

A direct economic impact which arises from the temporary shutdown of NPE-dependent chromatography resins production lines in Uppsala are the lost profits related to the sales of NPE-dependent chromatography resins.

As mentioned in Section 2.4.1, in 2017 the production of NPE-dependent chromatography resins at the facility in Uppsala generated approximately [redacted]. In order to proceed with the calculations, it is necessary to consider that:

- The future amount of revenues ([redacted]) to be generated with the sales of NPE-dependent chromatography resins in the period from 2021 to 2032 have been forecasted. Those revenues have been converted to Euros using an exchange rate of 1 EUR = 1.1609 USD as of September 3rd, 2018. As it can be seen, sales revenues are expected to increase year after year especially due to the increasing demand NPE-dependent chromatography resins by the pharmaceutical industry.
- The Applicant is making efforts to substitute emulsifiers containing NPE. Therefore, the foregone revenues due to a non-granted authorisation will be reduced year after year as substitution moves further.
- The average of the operating net profit for the period 2014-2017 has been calculated ([redacted]) to estimate the lost profits during the time need to implement an alternative in case of a non-granted authorisation.
- The lost profits are calculated based on the Net Present Value (NPV) of the forecasted profits during the period from 2021 to 2032 and using a discount rate of 4% a year.

Given these considerations, the calculation of lost profits is shown in Table 18.

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]

As shown above, the amount of lost profits if only losses in 2021 are considered will reach approximately [redacted]. If the entire applied for review period is considered (12 years), lost profits will amount to [redacted].

4.4 Reduction of R&D investments

Since in the NUS 4 (most-realistic NUS) the overall profitability of the Uppsala site would be impacted, R&D investments would decrease significantly which would have an impact on highly skilled employees and numbers of new product introduction (NPI) projects run. Hence, during the timeframe of implementation of an alternative emulsifier while the affected products are stopped in manufacturing, several NPIs would be missed. Those NPIs would

most likely be enablers for the biopharma customers, so the wider socio-economic impact would reach far beyond the impact on the Applicant. This impact is however difficult to monetise.

4.5 Environmental benefits

Since the production of NPE-dependent chromatography resins at Uppsala site will be stopped at the sunset date (in case of a non-granted authorisation), a maximum of [redacted] of NPE would no longer enter the environment via wastewater emissions on an annual basis (approximately [redacted] over 12 years) and until an alternative is fully implemented.

As calculated in the section 2.6.2.3, if it is accepted that a monetary figure per kg of NPE emissions can be used as an auxiliary measure for the assessment of environmental impacts, the monetised impact of the avoided emissions would vary between [redacted] and [redacted]

4.6 Distributional impacts

Severance payments that would have to be paid to the dismissed workers in EEA are also considered to be distributional impacts in EEA. Such distributional impacts, as per their definition, have not been included in the final assessment of impacts.

4.7 Uncertainty analysis

The ECHA Guidance on SEA (16) proposes an approach for conducting the uncertainty analysis. This approach provides three levels of assessment that should be applied if it corresponds to:

- qualitative assessment of uncertainties;

- deterministic assessment of uncertainties;

- probabilistic assessment of uncertainties.

The ECHA Guidance further states: the level of detail and dedicated resources to the assessment of uncertainties should be in fair proportion to the scope of the SEA. Further assessment of uncertainties is only needed if the assessment of uncertainties is of crucial importance to the overall outcome of the SEA.

Hence, only a qualitative assessment of uncertainties has been conducted to summarize and describe potential sources of uncertainty related to the impact categories. Since a deterministic probabilistic assessment of uncertainties would not be of significant importance for the overall outcome of the SEA, this assessment has not been carried out in this SEA.

Table 19 illustrates the systematic identification of uncertainties related to economic and environmental impacts.

Table 19: Uncertainties on economic and environmental impacts.

Identification of uncertainty	Evaluation (overestimation or underestimation)	Contribution to change of the SEA overall outcome
Impacts to biopharmaceutical manufacturers and patients have not been monetised	Only impacts to the applicant and dismissed workers have been monetised. Socioeconomic impacts are therefore higher than what is reflected in the figures used for the conclusions (e.g. cost-effectiveness ratio) **Underestimation of monetised socio-economic impacts of a non-granted authorisation**	**Negligible – this uncertainty cannot change the overall outcome of this SEA**
Since market growth and success of substitution efforts are unknown, NPE emissions to the environment during the entire review period have been assessed based on a worst-case scenario that is foreseen to occur during the entire review period	Emissions to the environment during the review period will be lower than considered for the impact assessment **Overestimation of environmental benefits of a non-granted authorisation**	**Negligible – this uncertainty cannot change the overall outcome of this SEA**
Environmental impacts have been assessed on the basis of NPE	Since volume of NPE emissions (and not NP) have been considered in the impact assessment, endocrine disrupting risks to environment have been certainly overestimated. **Overestimation of environmental impacts of a non-granted authorisation**	**Negligible – this uncertainty cannot change the overall outcome of this SEA**

None of the identified uncertainties has the potential to change the outcome of the SEA but actually show the robustness of the conclusions derived from this SEA (underestimation of socio-economic impacts and overestimation of environmental benefits of a non-granted authorisation).

5 CONCLUSIONS

5.1 Comparison of the benefits and risks

Table 20 summarizes the effects of a non-granted authorisation and applied for use scenario for a 12-year period corresponding to the review period applied for.

Table 20: Comparison of impacts for the applied for use and the non-use scenario.

Type of impact	Applied for use scenario	Non-use scenario(s)
Environment	• Up to [redacted] of NPE emissions annually (worst-case of [redacted] over 12 years)	• No emissions of a maximum of [redacted] of NPE over 12 years
Socio-economic impacts	• Guaranteed supply of chromatography resins to the biopharmaceutical and food sectors, ensuring a stable global production of APIs and safety of food products • Smooth transition of the Applicant from NPE-dependent chromatography resins production to a NPE-free process • Employment of at least [redacted] (and up [redacted]) workers related the production of the affected resins.	• Supply interruption of chromatography resins to the biopharmaceutical and food sectors, affecting ultimately millions of patients and consumers • Losses to the Applicant in terms of profits • Dismissals of up [redacted] workers and a minimum of [redacted]

Table 21 below summarizes the impacts for the applied for use and the non-use scenario in terms of costs and benefits which were calculated in section 4.

Table 21: Quantitative comparison of impacts.

Type of impact	Lower bound scenario	Upper bound scenario
Potential environmental benefits associated with a non-authorisation	**50 – 200 kg** [redacted] NPE emissions over 12 years = [redacted]	**50 – 200 kg** [redacted] NPE emissions over 12 years = [redacted]
Negative socioeconomic impacts associated with a non-granted authorisation	• Foregone profits amounting to **EUR 50-200 million** ([redacted]) • **Dismissal of 10-100 workers** [redacted] **→ EUR 1-11 million** [redacted] in social costs **Total = EUR 50-211 million** [redacted]	• Foregone profits amounting to **EUR 0.5-1.5 billion** ([redacted]) • **Dismissal of 100-500 workers** [redacted] **→ EUR 11-50 million** [redacted] in social costs **Total = EUR 0.5-1.6 billion** [redacted]
Ratio – socioeconomic impacts per Kg of avoided NPE emissions	**EUR 0.5-4 million** [redacted]	**EUR 1-10 million** [redacted]

5.2 Information for the length of the review period

The Applicant foresees a timeframe of 12 years for achieving full transition into an NPE-free manufacturing process for all its chromatography resins in scope of this AfA. This period is aligned with the expected R&D activities that will have to be completed for fully implementing an alternative (refer to section 3.4).

The review period applied for is in line with the Applicant's commitment to develop more environmentally-friendly processes by gradually transitioning into an NPE-free process in a feasible manner. Because no feasible alternative has been identified at present, further research must be carried out to evaluate the performance of potential alternatives in the current process and, once a feasible alternative(s) is identified, to implement it in the manufacturing of the impacted chromatography resins. As discussed, implementation of an alternative will be carried out in a staggered manner, due to technical and economic considerations. Parallel substitution is not feasible due to the existing uncertainties regarding an alternative feasibility and the possibility of failure. Instead, the Applicant will substitute NPE containing emulsifiers in the

manufacturing process of those resin families that currently constitute the largest volumes and will sequentially implement an alternative according to this prioritization. Substitution of emulsifiers containing NPE can only be considered successful if it is demonstrated that the performance of the resins produced with the new emulsifier(s) is the same as those produced with the current process. Additional time might be required for customers to evaluate these changes, so the 12 years described in this report only include the time required for transitioning into an NPE-free process at the manufacturing level.

In conclusion, the current status of the substitution plan shows that a review period of 12 years is needed until complete substitution of NPE containing emulsifiers in all impacted product groups of GEHC LS's chromatography resins is achieved. Once identified, an alternative must be implemented and optimized for the specific process of each different chromatography resin type. Because these products are mostly used in the biopharmaceutical industry for the production of human therapeutics, it is of utmost importance to ensure that this process change will have no impact on the performance of the finished chromatography resins and, therefore, on the biopharmaceutical production process. This requires considerable testing and validation.

Moreover, it has been clearly shown that the remaining risks are low, and the socio-economic benefits associated with the continued use of NPE containing emulsifiers in this use are high (more than [redacted] per kg of NPE emissions).

5.3 Substitution efforts taken by the Applicant if an authorisation is granted

The Applicant's activities for substituting NPE containing emulsifiers in its manufacturing process of chromatography resins have been ongoing since 2003. In this time, extensive R&D has been carried out leading to the identification of candidate alternatives that could potentially replace NPE containing emulsifiers in the production of chromatography resins. As described in section 3.1, further R&D efforts are needed to address the suitability of these alternatives. From the necessary steps required for the implementation of an alternative, initial activities for the first product family have already been completed. However, further testing is still needed before achieving full substitution.

If an authorisation is granted, the Applicant will follow its staggered substitution strategy over the next decade. Ongoing activities aim to assess the impact of replacing NPE based emulsifiers in the current manufacturing of NPE-dependent chromatography resins and the establishment of robust manufacturing processes. These activities include the study of the design conditions under which emulsifiers impact intrinsic resin product properties, the development of analytical methods to measure the concentration of emulsifier throughout the process, the testing of the prioritized alternatives at a pilot scale, and the development of an implementation plan for new process equipment that would reduce the consumption of solvents and emulsifiers.

Once these activities are completed, the full-scale implementation of the identified alternative will take place. Importantly, these activities must be carried out for each product family, so implementation of an alternative will be conducted in a sequential (staggered) manner. This

means that once an alternative has successfully passed from development phase to the validation phase for one product family, the development phase of the next product family can be initiated. All these tasks will have to be repeated in the next resin family group, following the prioritization matrix developed. Full substitution will then be achieved once an alternative has been implemented for all product families. A summary of the activities described above is provided in section 3.4. Considering these efforts, the Applicant foresees a time of 12 years for completing all activities required for a full transition to an alternative.

6 REFERENCES

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ANNEX A – Full list of considered potential alternatives

Trade Name	Chemistry
Akoline PGPR	Polyglyceryl-3 Polyricinoleate
Akoline MD50	Glyceryl Stearate
Acconon® SA-2	Ethoxylated Stearyl Alcohol
Yelkin ® series	Modified soy lecithin
Thermolec ® series	Modified soy lecithin
Ultralec series®	Modified soy lecithin
Beakin ® series	Modified soy lecithin
Armeen 16	Hexadecylamine
Armeen HTD	Hydrogenated tallowalkylamines
Armeen HT	Hydrogenated tallowalkylamines
Armeen OD	Oleyamine
Armeen 18D	Oleyamine
Armeen DM series	Monoalkyl dimethylamines
Elfacos E200	METHOXY PEG-22/DODECYL GLYCOL COPOLYMER
Berol® 260 SA	C9-11 alcohol 4EO (narrow range)
Berol 050	C12-16 alcohol 3 EO
Witconol NP-40	NonylPhenol (4 EO) Ethoxylate
Ethylan 1206	C10-12 Alcohol Ethoxylate/Propoxylate
Ethylan 324	Dipropeleneglycol EO/PO copolymer
Emulpon C0-100	Castor Oil (10 EO) ethoxylate
Emulpon C0-200	Castor Oil (20 EO) ethoxylate
Witconol 14	Polyglycerol oleate
Amadol 272	Modified Cocoamide diethanolamine (DEA)
Amadol 511	TOFA fatty Alkanolamide
Elfacos ST9	PEG-45/DODECYL GLYCOL COPOLYMER
Lutensol TO 3	c13 Oxo alcohol ethoxylated
Lutensol XP 30	C10-Guerbet alcohol ethoxylates
Lutensol ON 30	C10-Oxo alcohol ethoxylate
Dehydol D 3	decyl alcohol + approx. 3 EO
Emulan A	oleic acid ethoxylate
Lutensol TO 2	c13 Oxo alcohol ethoxylated
Dehymuls® PGPH	Polyglyceryl-2 Dipolyhydroxystearate
Lameform® TGI	Triglycerine diisostearate
CremerCOOR GMO 90	glyceryl oleate
CREMERCOOR® PG3 DIS	Polyglyceryl-3 Diisostearate
IMWITOR® 600	Polyglyceryl-3 Polyricinoleate
Arlacel 83	SORBITAN SESQUIOLEATE
GRINDSTED® SSL /CSL	Calcium Stearoyl Lactylate

Trade Name	Chemistry
GRINDSTED® LACTEM lactic acid esters	Lactic acid esters of MG
GRINDSTED® MONO-DI	mono-diglycerides
GRINDSTED® ACETEM	Acetic acid esters of monoglycerides
GRINDSTED® PGMS	Propylene Glycerol Ester
Dermofeel® GO soft	Polyglyceryl-2 Sesquioleate
Dermofeel® PGPR	Polyglyceryl-3 Polyricinoleate
Symbio® muls WO	Polyglyceryl-3 Polyricinoleate, Sorbitan Sesquioleate, Cetyl Ricinoleate, Glyceryl Caprate, Cera Alba, Magnesium Stearate, Aluminium Tristearate
Plurol® Diisostearique CG	Polyglyceryl-3 Diisostearate
Apifil®	PEG-8 beeswax
Capryol™ 90	Propylene glycol monocaprylate (type II) NF
Capryol™ PGMC	Propylene glycol monocaprylate (type I) NF
Labrafil® M2130CS	Lauroyl macrogol-6 glycerides EP Lauroyl polyoxyl-6 glycerides NF, Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Labrafil® M2125CS	Linoleoyl macrogol-6 glycerides EP Linoleoyl polyoxyl-6 glycerides NF; CORN OIL PEG-6 ESTERS (FDA IIG)
Labrafil® M1944CS	Oleoyl macrogol-6 glycerides EP Oleoyl polyoxyl-6 glycerides NF ; Apricot kernel oil PEG-6 esters (USA FDA IIG) PEG-5 OLEATE (FDA IIG)
Hetan S S	SORBITAN STEARATE
Hetan S O	SORBITAN OLEATE
Gransurf 50C	Dimethicone (and) PEG/PPG-18/18 dimethicone
Gransurf 50C-HM	Dimethicone (and) PEG/PPG-18/18 dimethicone
HallStar® GDL	Glyceryl dilaurate
HallStar® GMO	Glyceryl oleate
TERSPERSE®2510	Polycondensed fatty acid/alkylene oxide adduct
TERSPERSE®2520	Modified polyester condensate
TERSPERSE®4890	Polymeric amine condensate
Hydriol® PGDI	Polyglyceryl Diisostearate
Hydriol® PGSI.2	Polyglyceryl-2 Sesquiisostearate
Rheodol SP-P10	Sorbitan palmitate
Rheodol AS-10V	SORBITAN STEARATE
Sorbirol O	Sorbitan monooleate
Kosteran I-1	Sorbitan isostearyl ester
Kosteran O-1 VL	Sorbitan oleyl ester
Kosteran P-1 G	Sorbitan palmityl ester

Trade Name	Chemistry
Kosteran S-1 G	Sorbitan stearyl ester
Lipoid ® series	Lethin, Phospholipids and compunds with phosphatidylcholine
Lonzest® SOC	Sorbitan, (Z)- 9- octadecenoate (2:3)
Lonzest® SMP	Sorbitan palmitate
NIAPROOF® Calcium Stearoyl Lactylate	Calcium Stearoyl Lactylate
Radiasurf® 7145	Sorbitan Trioleate
Radiamuls® 2155	Sorbitan Trioleate
SIMALINE WO	PEG-30 Dipolyhydroxystearate
EASYNOV	Octyldodecanol & Octyldodecyl Xyloside & PEG-30 Dipolyhydroxystearate
FLUIDANOV 20X	Octyldodecanol & Octyldodecyl Xyloside
Silok® 2215	Cetyl PEG/PPG-10/1 Dimethicone/Isooctyl Palmitate
Sisterna SP30	Sucrose Distearate
Sisterna SP10	Sucrose Polystearate
Crodafos O10A	Oleth-10 Phosphate
Crodafos™ CS2A	Ceteareth-2 Phosphate
Crodafos™ O3A	Oleth-3 Phosphate
Crodafos SG-LQ-(RB)	PPG-5-Ceteth-10 Phosphate
Lubrhophos LF-800	C10-16 ethoxylated propoxylated phosphate
Lubrhophos LB-400	Polyoxyethylene oleyl ether phosphate
Rhodafac PA/32	Polyoxyethylene monooleyl ether phosphate
Rhodafac PA/35	Polyoxyethylene monooleyl ether phosphate
Sensanov WR	C20-22 Alkyl Phosphate & C 20-22 Alcohols
Lakeland PAE 176	Phosphate ester of ethoxylated heptadecanol 6 EO
Lakeland PAE 185	Phosphate ester of ethoxylated octadecanol 5 EO
Rhodafac RM-510	Phosphate ester of dinonyl phenol ethoxylate
Hostaphat® CC 100	Cetyl phosphoric acid ester, acid form,mono/diester
Hordaphos® MDAH	Mono-/di-2-ethylhexyl phosphoric acid ester, acid form
Hostaphat® 1306	Isotridecyl polyoxethyl (6 EO) phosphoric acid mono/diester, acid form
Hostaphat® KL 340 D	Lauryl polyethoxy (4 EO) phosphoric acid ester, sodium salt, mono/di/triester
Hostaphat® KW 340 D	Stearyl polyethoxy (4 EO) phosphoric acid ester, sodium salt, mono/di/triester
Hordaphos 145	Oleyl polyoxethyl (5 EO) phosphoric acid mono/diester, acid form
Phospholan PE169	Mono/di phosphate ester, ethoxylated. Free alcohol ethoxylate present.
Phospholan PE65	Anionic alkyl phosphate ester, free acid
Phospholan PHB14	Phenol ethoxylate phosphate ester
SPAN 60	Sorbitan stearate

Trade Name	Chemistry
SPAN 80	Sorbitan oleate
SPAN 120	Sorbitan Isostearate
Dehymuls PGPH	Polyglyceryl-2 Dipolyhydroxystearate
FLUIDANOV 20X	Octyldodecanol & Octyldodecyl Xyloside
Prisorine 3700	Polyglycerol 3 Diisostearate
Isolan IS	Methyl Glucose Isostearate
Ethyl cellulose N50	Ethyl cellulose N50
Crodesta F50	Sucrose distearate
Geropon DOS	Sodium dioctylsulfosuccinate
Elfacos E200	Methoxy PEG-22/Dodecyl glycol copolymer

ANNEX B – Prioritization matrix

Technical Alternatives	Chemically stable	Easy to analyze	No crosslinking	Emulsified bead appearance	Emulsification efficiency	Stable beads during cooling	Comparable bead matrix properties	Easy to remove in washing	Emulsification PSD	Process impact of lot-to-lot variation (emulsifier)	Row Total	Relative Value
Criteria Weights	*0.02*	*0*	*0.04*	*0.13*	*0.03*	*0.14*	*0.23*	*0.13*	*0.13*	*0.14*		
(Alternative Emulsifier A)	**0.00**	**0.00**	**0.01**	**0.06**	**0.00**	**0.05**	**0.06**	**0.03**	**0.01**	**0.04**	0.26	**0.2565**
(Alternative Emulsifier B)	**0.01**	**0.00**	**0.01**	**0.01**	**0.00**	**0.00**	**0.06**	**0.03**	**0.06**	**0.04**	0.21	**0.2122**
(Alternative Emulsifier C)	**0.01**	**0.00**	**0.01**	**0.01**	**0.02**	**0.05**	**0.06**	**0.03**	**0.06**	**0.04**	0.27	**0.2748**
(Alternative Emulsifier D)	**0.00**	**0.00**	**0.01**	**0.06**	**0.00**	**0.05**	**0.06**	**0.03**	**0.01**	**0.04**	0.26	**0.2565**

Performance Values of NPE	
10 = Much better	10
5 = Better	5
1 = Equal	1
1/5 = Worse	0.2
1/10 = Much worse	0.1

Figure 22[#8]: Overview of the prioritization matrix used by the Applicant for shortlisting the alternative emulsifier candidates. NPE is used as comparison for the assessment of the alternatives

ANNEX C – Safety Data sheet: [redacted]

ANNEX D – Safety Data Sheet: [redacted]

ANNEX E – Safety Data Sheet: [redacted]

ANNEX F – Safety Data Sheet: [redacted]