Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-Nonylphenol, branched and linear, ethoxylated (4-NPnEO)

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

Submitting applicant

Cytiva Sweden AB[1]

ECHA/RAC/SEAC: AFA-O-0000006752-71-01/D

Consolidated version

Date: 18/06/2020

[1] The name of the submitting applicant in the original application was GE Healthcare Bio-Sciences AB. Due to a notified change of corporate name, this was updated to Cytiva Sweden AB.

Consolidated version of the Opinion of the Committee for Risk Assessment and Opinion of the Committee for Socio-economic Analysis on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to the following application for authorisation:

Applicant	**Cytiva Sweden AB** (position in supply chain: downstream)
Substance ID EC No CAS No	**4-Nonylphenol, branched and linear, ethoxylated (in what follows referred to as 4-NPnEO)** - -
Intrinsic properties referred to in Annex XIV	☐Carcinogenic (Article 57(a)) ☐Mutagenic (Article 57(b)) ☐Toxic to reproduction (Article 57(c)) ☐Persistent, bioaccumulative and toxic (Article 57(d)) ☐Very persistent and very bioaccumulative (Article 57(e)) ☒Other properties in accordance with Article 57(f) - Endocrine disrupting properties - environment
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**
	Other connected uses: Not applicable
	Same uses applied for: Not applicable
Use performed by	☒ Applicant ☐ Downstream User(s) of the applicant
Use ID (ECHA website)	0172-01
Reference number	11-2120816866-44-0001
RAC Rapporteur	DUNAUSKIENĖ Lina
SEAC Rapporteur	BRIGNON Jean-Marc

SEAC Co-rapporteur	DOMINIAK Dorota
ECHA Secretariat	GMEINDER Michael LEFEVRE Rémi MÁK Éva

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	21/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	02/08/2019
Application has been submitted by the Latest Application Date for the substance and applicant can benefit from the transitional arrangements described in Article 58(1)(c)(ii)	☒Yes ☐No
Consultation on use, in accordance with Article 64(2): https://echa.europa.eu/applications-for-authorisation-previous-consultations	14/08/2019-09/10/2019
Comments received	☐Yes ☒No Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23851/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Request for additional information in accordance with Article 64(3)	13/09/2019 (RAC and SEAC) 28/11/2019 (RAC) Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23851/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	Not held – Not needed considering no new information submitted in the consultation and responses of applicant to RAC and SEAC requests for additional information.

Extension of the time limit set in Article 64(1) for the sending of the draft opinion to the applicant	☐Yes ☒No
The application included all the necessary information specified in Article 62 that is relevant to the Committees' remit	☒Yes ☐No
Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	RAC: 13/03/2020, agreed by consensus.
	SEAC: 05/12/2019, agreed by consensus.
Date of sending of the draft opinion to applicant	11/05/2020
Date of decision of the applicant not to comment on the draft opinion, in accordance with Article 64(5)	18/06/2020
Date of receipt of comments in accordance with Article 64(5)	Not relevant
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 18/06/2020, adopted by consensus.
	SEAC: 18/06/2020, adopted by consensus.
Minority positions	RAC: ☒N/A
	SEAC: ☒N/A

THE OPINION OF RAC

RAC has formulated its opinion on:

- the risks arising from the use applied for,
- the appropriateness and effectiveness of the risk management measures described, as well as
- other available information.

In this application, the applicant did not derive PNEC(s). Therefore, RAC concluded, in accordance with Annex I of the REACH Regulation, that for the purposes of the assessment of this application it was not possible to determine PNEC(s) for the endocrine disrupting properties for the environment of the substance.

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

RAC concluded that the operational conditions and risk management measures described in the application are **not** appropriate and effective in limiting the risk. The proposed additional conditions for the authorisation are expected to result in operational conditions and risk management measures that are appropriate and effective in limiting the risk. The proposed monitoring arrangements for the authorisation are expected to provide information on the trends in emissions over the authorisation period. This information should also be included in the review report.

The recommendations for the review report are expected to allow RAC to evaluate the review report efficiently.

The use applied for may result in emissions of the substance to the environment of up to 14.4 kg/year.

THE OPINION OF SEAC

SEAC has formulated its opinion on:

- the socio-economic factors, and
- the suitability and availability of alternatives associated with the use of the substance as documented in the application, as well as
- other available information.

SEAC took note of RAC's conclusion that it is not possible to determine a PNEC for the endocrine disrupting properties for the environment of the substance in accordance with Annex I of the REACH Regulation.

The following alternatives have been assessed (see Section 4 of the justifications to this opinion):

- Four different phosphate ester emulsifiers, exact chemical names claimed confidential by the applicant.

SEAC concluded on the analysis of alternatives and the substitution plan that:

- By the Sunset Date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant.

- The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

SEAC concluded on the socio-economic analysis that:

- The expected socio-economic benefits of continued use are at least €43-136 million (over the 12-year assessment period) and additional benefits to society have been assessed qualitatively but have not been monetised. These additional benefits comprise, in particular, avoided economic impacts on more than 70 biopharmaceutical manufacturers using the affected chromatography resins as well as avoided impacts on patients due to the unavailability of more than 190 human therapeutics and vaccines.
- Risks to the environment of shortlisted alternatives have not been quantified. There may therefore be a risk arising due to the use of an alternative should the authorisation not be granted.

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance.

SEAC considered that if an authorisation was refused, the use of the substance could:

- cease altogether
- be substituted by market actors operating inside the EU
- be taken up by market actors operating outside the EU

SEAC considered that, if an authorisation was refused, it was likely that in the European Union:[2]

- 10-100 jobs would be lost

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

Additional conditions for the authorisation or monitoring arrangements are proposed. These are listed in sections 7 and 8 of the justification to this opinion.

Recommendations for the review report are made. These are listed in section 9 of the justification to this opinion.

REVIEW PERIOD

Taking into account the information provided in the application for authorisation submitted by the applicant, a **12-year** review period is recommended for this use.

[2] Wherever reference is made to the European Union, this shall apply also to EEA countries.

SUMMARY OF THE USE APPLIED FOR

Role of the applicant in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ downstream user
Number and location of sites covered	1 site in Uppsala, Sweden
Annual tonnage of Annex XIV substance used per site (or total for all sites)	< 1 tonne/year
Function(s) of the Annex XIV substance	The emulsifiers containing 4-NPnEO fulfil the following key functionalities in the manufacturing of the 13 intermediate resins: reduction of interfacial tension to facilitate emulsion droplet formation with low defect contents; facilitation of droplet size reduction to reach the targeted drop size distribution; droplet stabilization during cooling and particle formation to minimize particle defects; low interference with process conditions and other processing aids.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	The emulsifiers containing 4-NPnEO are used in the manufacturing of 13 intermediate resins for the further production of more than 120 chromatography resins which are used in biopharmaceutical applications for the manufacture and purification of active pharmaceutical ingredients (APIs) and for research and development activities, in analytical applications for the characterization and development of analytical methods for biomolecules and polymers, in the food and beverages industry (e.g. to detect food additives), and in nutraceuticals and nutritional chemistry.
Shortlisted alternatives discussed in the application	Alternative substances considered: Four different phosphate ester emulsifiers, exact chemical names claimed confidential by the applicant.
Annex XIV substance present in concentrations above 0.1 % in the products (e.g. articles) made	☐Yes ☒No ☐Unclear ☐Not relevant
Releases to the environmental compartments	☒Water ☐Air

	☐Soil ☐None
The applicant has used the PNEC recommended by RAC	☐Yes ☐No ☒Not relevant
All endpoints listed in Annex XIV were addressed in the assessment	☒Yes ☐No
Adequate control demonstrated by applicant for the relevant endpoint(s)	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of (combined, daily / shift-long) exposure/release used by applicant for risk characterisation	Environment: • Water: 14.4 kg/year (based on measured data from 2018 in the waters from on-site WWTP) • Air: 0 kg/year • Soil: 0 kg/year
Risk Characterisation	Environmental compartments: The applicant has treated 4-NPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. RAC concluded that the applicant has not demonstrated that its releases of 4-NPnEO to the environment have been prevented or minimised as far as technically and practically possible.
Applicant is seeking authorisation for the period of time needed to finalise substitution (‘*bridging application*’)	☒Yes ☐No ☐Unclear
Review period argued for by the applicant (length)	12 years
Most likely Non-Use scenario	Temporary shutdown of the manufacturing of chromatography resins dependent on intermediate resins manufactured using 4-NPnEO containing emulsifiers until an alternative is developed and implemented.
Applicant concludes that benefits of continued use outweigh the risks of continued use	☒Yes ☐No

	☐Not Applicable – threshold substance with adequate control
Applicant's benefits of continued use As recalculated by SEAC	Avoided profit loss: €42-125 million (over the 12-year assessment period)
Society's benefits of continued use As reported by the applicant	Avoided job loss: €1-11 million (over the 12-year assessment period) Avoided economic impacts (revenue losses, penalties, reputational damage) on > 70 biopharmaceutical manufacturers using the affected chromatography resins Avoided impacts on patients due to unavailability of > 190 human therapeutics and vaccines Avoided wider socio-economic impacts due to applicant's reduction of R&D investments
Distributional impacts if authorisation is not granted	Not reported by the applicant
Job loss impacts if authorisation is not granted As reported by the applicant	10-100

SUMMARY OF RAC AND SEAC CONCLUSIONS[3]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

RAC observes that relevant solid and liquid wastes are collected for treatment by incineration. Residual releases of 4-NPnEO to the environment originate from emulsifier residues in the waste water from the production and cleaning processes. RAC notes that the applicant has assessed the technical viability of additional operational conditions (OCs) and/or risk management measures (RMMs) needed to ensure a complete collection of 4-NPnEO. RAC is of the opinion that the OCs and RMMs in the exposure scenario are not appropriate and effective in limiting the risk.

Are the OCs/RMMs in the Exposure Scenario appropriate and effective in limiting the risk?

☐Yes ☒No

Does RAC propose additional conditions related to the operational conditions and risk management measures for the authorisation?

☒Yes ☐No

Does RAC propose monitoring arrangements related to the operational conditions and risk management measures for the authorisation?

☒Yes ☐No

Does RAC make recommendations related to the operational conditions and risk management measures for the review report?

☒Yes ☐No

2. Exposure Assessment

Exposure level used by RAC for risk characterisation:

Releases to the environmental compartments

Water: 14.4 kg/year (based on measured data from 2018 in the waters from on-site WWTP)
Air: 0 kg/year
Soil: 0 kg/year

Conclusions of RAC

RAC considers that the exposure estimates provided by the applicant are appropriate. RAC

[3] The numbering of the sections below corresponds to the numbers of the relevant sections in the Justifications.

did not identify shortcomings in the methodology used that would invalidate this conclusion.

Does RAC propose additional conditions[4] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC propose monitoring arrangements[5] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to exposure assessment for the review report?

☐Yes ☒No

3. Risk Characterisation

Conclusions of RAC

RAC is of the view that the applicant has not demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible (with a view to minimising the likelihood of adverse effects).

4. Analysis of alternatives and substitution plan[6]

What is the amount of substance that the applicant uses per year for the use applied for?

< 1 tonne/year

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

Has the applicant submitted a substitution plan?

☒Yes ☐No

[4] Conditions can be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

[5] Monitoring arrangements can be recommended where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but minor concerns were identified.

[6] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be "*in abstracto"* or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

Conclusions of SEAC

By the sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant. The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

Does SEAC propose any additional conditions or monitoring arrangements related to the assessment of alternatives for the authorisation?

☐Yes ☒No

Does SEAC make any recommendations to the applicant related to the content of the potential review report?

☐Yes ☒No

5. Benefits and risks of continued use

Has the applicant adequately assessed the benefits and the risks of continued use?

Conclusions of SEAC:

☒Yes ☐No

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- SEAC's assessment of the availability, technical and economic feasibility of alternatives,
- additional information provided by the applicant,
- RAC's assessment of the risks to the environment.

6. Proposed review period for the use

☐ 4 years

☐ 7 years

☒ 12 years

☐ Other – … years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For the environment ☒Yes ☐No

SEAC

Additional conditions: ☐Yes ☒No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For the environment ☒Yes ☐No

SEAC

Monitoring arrangements ☐Yes ☒No

9. Recommendations for the review report

RAC

For the environment ☒Yes ☐No

SEAC

AoA ☐Yes ☒No

SP ☐Yes ☒No

SEA ☐Yes ☒No

10. Applicant's comments on the draft opinion

Has the applicant commented the draft opinion?

☐Yes ☒No

Has action been taken resulting from the analysis of the applicant's comments?

☐Yes ☐No ☒Not applicable

JUSTIFICATIONS

0. Short description of use

Cytiva Sweden AB applied for the industrial use of emulsifiers containing nonylphenols ethoxylated (hereafter referred to as 4-NPnEO) for the manufacture of chromatography resins which are used in the biopharmaceutical industry, the food & beverage sector and by academia. More specifically, 4-NPnEO is present as a process agent in four different emulsifiers (referred to as "emulsifiers A to D") used in the manufacturing of 13 intermediate resins for the further production of more than 120 chromatography resins. The use takes place at one site in Uppsala, Sweden. The total maximum usage of 4-NPnEO in the facility is envisaged to be < 1 tonne/year[7] and the maximum foreseen emissions are estimated at 14.4 kg/year (which corresponds to 173 kg over the requested 12-year review period). According to the applicant 4-NPnEO is not present in the end products (chromatography resins) and there are no further downstream users of 4-NPnEO in the applicant's supply chain.

0.1. Description of the process in which Annex XIV substance is used

During the production of intermediate resins, emulsifiers containing 4-NPnEO at different concentrations are added in the emulsification step to aid in the formation of aqueous droplets dispersed in a solvent phase. A subsequent reduction of temperature triggers the solidification of the droplets and thereby the formation of porous polysaccharide-based particles. A series of washing steps follows to remove all residuals of emulsifiers and solvents from the particles. The washed particles correspond to the intermediate resin product, which is then further used for downstream processing. The size, shape and physical properties of these particles determine the characteristics of the different chromatography end products. It is the combination of the emulsifier design (i.e. composition, incl. concentration of 4-NPnEO) and of the production process that defines the final particle distribution of the intermediate resin, which in turn determines the characteristics and quality of the final resin. The emulsifiers containing 4-NPnEO are considered processing aids that are removed during the manufacturing process and are thus not part of the final chromatography resins.

Table 1: Contributing Scenarios presented in the Use

Contributing scenario	ERC/PROC	Name of the contributing scenario
ECS 1	ERC 4	Environmental emissions from the on-site WWTP
WCS 1	PROC 9	Receipt of raw material and storage – sampling for quality test
WCS 2	PROC 9	Transfer into smaller containers
WCS 3	PROC 4	Charging production vessel
WCS 4	PROC 1	Chromatography resin production
WCS 5	PROC 8b	Waste management – emptied emulsifier containers
WCS 6	PROC 1, PROC 8b	Process waste management
WCS 7	PROC 28	Cleaning and maintenance
WCS 8	PROC 9, PROC 15	NPE sampling

[7] The applicant has claimed that disclosure to the general public of the actual value would undermine the protection of its commercial interests. The applicant has nevertheless disclosed the actual value to RAC and SEAC.

Receipt of raw material and storage – sampling for quality test

The substance is delivered in 5 L containers (emulsifier D) or 200 L barrels (emulsifiers A, B and C). Upon arrival to the Uppsala site, the content of each barrel undergoes quality control testing (QC test). If whole barrels fail the QC test upon arrival to the site due to damage to the product during transportation (e.g. due to wrong temperature conditions, etc.), the whole barrel is disposed of as hazardous waste and sent for incineration. Emulsifiers are also QC tested for shelf life (they have up to one-year shelf life). The barrels with emulsifiers are stored in secondary containments until the first weighing.

Transfer into smaller containers

The content of the whole 200 L barrel is transferred to 15 L containers using a stainless steel valve. From December 2019 on, such transfer operations are done using disposable valves. From these containers, smaller volumes are weighed for production. For that, the emulsifier is poured from the 15 L containers into cans of different sizes (ca. 1-13 kg) using a disposable funnel.

Charging production vessel

During production, the emulsifiers containing 4-NPnEO are added to emulsification vessels to sustain stable emulsions. The plastic containers of emulsifiers are placed and secured upside down inside a stainless steel holder and then emptied into the reactor vessel.

Chromatography resin production

The emulsification reaction process occurs inside a closed vessel. After the emulsification step the base matrix is transferred into a washing vessel and is washed with solvent (ethanol) and/or water in several steps.

Cleaning and maintenance

All equipment that comes into contact with emulsifiers is cleaned thoroughly and it is only once the concentration of total emulsifier residues is below the detection limit of 1 mg/L that the waste water (be it from process, cleaning or maintenance operations) is released to the on-site waste water treatment plant (WWTP). In particular, the first washing water of the empty vessel after the emulsification step of the process is released to the next manufacturing process step, i.e. the washing of the resin particles. The water from the successive washing steps is sent to the carbon filter pre-treatment as long as it contains measurable emulsifier residues. Once below the detection limit, the washing water is directly released to the on-site WWTP, without pre-treatment.

0.2. Key functions and properties provided by the Annex XIV substance

The emulsifiers containing 4-NPnEO fulfil the following key functionalities in the manufacturing of the 13 intermediate resins:

- Reduction of interfacial tension to facilitate emulsion droplet formation with low defect contents;
- Facilitation of droplet size reduction to reach the targeted drop size distribution;
- Droplet stabilization during cooling and particle formation to minimize particle defects;
- Low interference with process conditions and other processing aids.

0.3. Types of products made with the Annex XIV substance and market sectors likely to be affected by the authorisation

The emulsifiers containing 4-NPnEO are used in the manufacturing of 13 intermediate resins fur the further production of more than 120 chromatography resins which are used in biopharmaceutical applications for the manufacture and purification of active pharmaceutical ingredients (APIs) and for research and development activities, in analytical applications for the characterization and development of analytical methods for biomolecules and polymers, in the food and beverages industry (e.g. to detect food additives), and in nutraceuticals and nutritional chemistry.

1. Operational Conditions and Risk Management Measures

The applicant presented one exposure scenario (ES 1: Industrial use of emulsifiers containing nonylphenols ethoxylated for the manufacture of chromatography resins used by the biopharmaceutical industry, food & beverage sector and academia) with one environmental contributing scenario (ECS 1: Environmental emissions from manufacture of chromatography resins – ERC 4 (Use of non-reactive processing aid at an industrial site)).

Eight worker contributing scenarios (WCS) are presented in the CSR. However, as the scope of the CSR is limited to the environmental risk of 4-NPnEO, WCS were not discussed in detail.

No contributing scenario for the service life is provided because, according to the applicant, the final product is not meant to contain 4-NPnEO.

1.1. Environment

Operational Conditions (OCs) and Risk Management Measures (RMMs) in place for control of emissions to:

Water

All process liquids that contain concentrations of emulsifier residues above the limit of 1 mg/L are sent to a carbon filter pre-treatment, which is claimed to have an abatement effectiveness of over 99%. When the level of emulsifier residues in the waste water from the production and production equipment cleaning processes are below 1 mg/L of the total emulsifier residues concentration, it is released to an on-site WWTP. Waste water leaving the site is discharged into a sewer and is going to a municipal sewage treatment plant (STP).

The applicant noted in the CSR that High-Performance Liquid Chromatography-Fluorescence Detection (HPLC-FLD) analysis was performed at the on-site laboratory on the effluent before filtration ("BF") and after filtration ("AF"). The analysis demonstrated that the removal of the total nonylphenol ethoxylates (i.e. nonylphenol ethoxylates (4-NPnEO) and dinonylphenol ethoxylates (DNPnEO)) was typically below the established analytical level of quantification (LOQ) of 0.1 mg/L. A new UHPLC Q-TOF (ultra-high performance liquid chromatography with quadrupole time-of-flight detection) method (LOQ of 2 µg/L) to quantify the content of 4-NPnEO and DNPnEO in waste water sludge was developed at Cytiva Sweden AB in 2015 and implemented in January 2016; measures conducted with this method confirmed the effectiveness of the implemented RMMs.

Air

According to the applicant, releases to air are not expected taking into account the activities performed (incl. manufacturing step in closed system) and the low vapour pressure of the

substance.

Soil

There are no direct releases to soil from the manufacturing site.

The on-site WWTP has no sludge separation, thus the water and sludge from the on-site WWTP go to the municipal STP.

Waste (solid and liquid)

- Barrels of 4-NPnEO containing emulsifiers that fail the QC test upon arrival or a test for shelf life are discarded and sent for incineration.
- Waste products that could be contaminated with 4-NPnEO (e.g. PPE, disposable pipettes, empty product containers, cans, funnels) are collected and incinerated in accordance with existing procedures.
- In case of spillage, all materials used for cleaning are collected and disposed of according to standard procedures for hazardous waste and incinerated by an authorized third-party waste vendor.
- In its answers to RAC questions the applicant confirmed that starting from December 2019, the stainless steel valve has been replaced by a disposable valve for the transfer of the emulsifier. After its use, the disposable valve is discarded as hazardous waste and incinerated by an authorized third-party waste vendor. Based on the mass balance analysis the applicant estimated that this improvement in transfer handling routines has led to an overall reduction of 10 % of the total yearly 4-NPnEO emissions.

Process Waste management

- Solvent recovery: The process is closed. All liquids are pumped to tanks and waste is pumped into tanker and sent for incineration. Washing liquids that contain emulsifier with 4-NPnEO in toluene is sent to pre-treatment after which the toluene is recycled, and the remaining washing liquid is sent to pre-treatment for emulsifiers (FBE – see hereafter). Washing liquids with ethanol that may contain 4-NPnEO are sent to a different mother liquid tank. Here, 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.

- Pre-treatment emulsifiers (FBE): The process water is pumped from the reaction vessel to a pre-treatment at the on-site WWTP, via 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 carbon is filtered out and the water is led to the biological treatment in the on-site WWTP. Water from this plant is discharged to a municipal STP.

- Used carbon filters are dried, collected in bags and disposed of according to standard procedures for hazardous waste and incinerated by an authorised third-party waste vendor.

Table 2: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Water	Incineration of solid and liquid waste Carbon filter pre-treatment of process waters	No residual releases assumed from solid and liquid waste that is collected for incineration. Water from all processes that contain measurable emulsifier residues are sent to the carbon filter pre-treatment, with effectiveness of over 99%. *Residual releases originate from waste water that is discharged to the biological treatment of the on-site WWTP:* • *after treatment with carbon filter, or* • *from cleaning processes directly (no carbon filter treatment), when emulsifier residues are below detection limit.*
Air	Closed system	Taking into account the activities performed the substance emissions to air compartment are not expected.
Soil	Controlled environment in the facility	There are no direct releases to soil from the manufacturing site.

Additional technical and organisational conditions and measures that are not mentioned above:

- The barrels with emulsifiers are stored in secondary containments until the first weighing.
- Standard operating procedures for management of wastes produced in the site.
- Training of personnel on handling and disposal of waste.
- An emergency plan is available for spill incidents.
- Maintenance procedures in place.

1.2. Discussion on OCs and RMMs and relevant shortcomings or uncertainties

All solid waste, which has been in contact with emulsifiers containing 4-NPnEO, is collected and disposed of as waste for incineration, as well as all remaining 4-NPnEO containing emulsifiers which have been unused or rejected after quality control.

All solid waste and liquid waste from the solvent recovery step is collected for incineration. All process and cleaning waters that contain measurable concentrations of emulsifier residues are sent to the carbon filter pre-treatment. Once the level of emulsifier residues in the waste water from the production and cleaning processes is below 1 mg/L, the waste water is released to on-site WWTP and eventually to municipal sewage system.

It should be noted that the applicant, in order to reduce the emissions of 4-NPnEO in cleaning water, has already modified the procedure of transferring emulsifier from barrels to smaller containers that has led to the reduction of emissions to the waste water by approximately 10%. The applicant also reported in the CSR that some releases of 4-NPnEO to the water could occur due to the emulsifier residues in the waste water from the production and cleaning processes even though such water is initially passed through the carbon filter. The applicant's analysis of additional OCs and/or RMMs needed to ensure a complete collection of 4-NPnEO is presented below:

1) In the answers to RAC questions, the applicant explained that in order to reduce emissions further it would require using emulsifier pre-treatment with active carbon for the large volumes[8] of washing water with residues below detection level. The applicant pointed out that in order to collect all process water potentially containing 4-NPnEO, the capacity of pre-treatment would need to increase about 8 fold from thousands to tens of thousands of cubic meters per year and would require significant investment[9] (in the order of tens of millions of euros). Besides, the applicant stressed that increasing the pre-treatment facility currently is practically not feasible since there is no space on the applicant's site to build such a facility. It is also not known if pre-treatment with active carbon will work satisfactorily with such low concentrations of 4-NPnEO. The applicant additionally pointed out that his site is located in an industrial area and there is no obvious availability of land around the site that could be acquired at commercially reasonable rates in order to build such a facility and building "on a green field" away from the site would require logistics solutions that are not practically feasible.
2) Other methods such as ion exchange and de-watering were also practically investigated, but the results did not lead to any improvements. Practical investigation of end-of-pipe solutions (after the biological treatment in the on-site WWTP) with a wider scope than only treating 4-NPnEO has also been performed by the applicant, including chemical oxidation, chemical precipitation, adsorption with active coal, filtration (Ultrafiltration + Nano Filtration/Reverse Osmosis) and evaporation but none of these techniques were found to be practically (waste water flow too large) or technically feasible (due to too low efficiency for reduction of Chemical Oxygen Demand).
3) The applicant also pointed out that another possibility to further reduce emissions would be to invest in an in-house sludge separation facility with a larger scope than only 4-NPnOE. Currently the on-site WWTP has no sludge separation, thus the water and sludge go to the municipal STP. The applicant noted that this type of investments would take at least 5 years to implement (including construction and commissioning) and would again require significant investments in the order of tens of millions of euros)[10]. As the applicant foresees achieving a full transition to 4-NPnEO free manufacturing process for all its chromatography resins in 12 years from the sunset date, the applicant considers that such an investment would not be practically justified.

RAC notes that the applicant has assessed the technical viability of the additional OCs and/or RMMs needed to ensure a complete collection of 4-NPnEO. RAC acknowledges that the information provided indicates that the implementation of most of the envisaged potential measures to reduce 4-NPnEO containing emulsifier residues in the waste water from the production and cleaning processes has technical and organisational restraints. RAC also notes that the applicant is planning to switch to a 4-NPnEO free manufacturing process within 12 years and is planning to reduce the use of the substance starting from 2022.

Nevertheless RAC also points out that up to 14.4 kg/year of 4-NPnEO are projected to be released from the on-site WWTP to the municipal sewer system (i.e. up to 173 kg in total over the requested 12-year review period). RAC also notes that, according to the information provided by the applicant, there are no actual technical restraints (only economic and organisational) which would impede the implementation of some additional measures (such as on-site sludge separation facility) to further reduce emissions of 4-NPnEO to the water compartment.

[8] Actual volumes are claimed confidential but are known to RAC.
[9] Actual investment costs are claimed confidential but are known to RAC.
[10] Actual investment costs are claimed confidential but are known to RAC.

Taking all of the above into account, RAC considers that the applicant has not demonstrated that the OCs and RMMs in the exposure scenario are appropriate and effective in limiting the risk and, as a result, proposes additional conditions and monitoring arrangements for the authorisation (see sections 7, 8 and 9).

1.3. Conclusions on OCs and RMMs

Overall conclusion

OCs and RMMs in the exposure scenario are not appropriate and effective in limiting the risk.

Are the operational conditions and risk management measures appropriate[11] and effective[12] in limiting the risk for workers, consumers, humans via environment and/or environment?

Workers	☐Yes	☐No	☒Not relevant
Consumers	☐Yes	☐No	☒Not relevant
Humans via Environment	☐Yes	☐No	☒Not relevant
Environment	☐Yes	☒No	☐Not relevant

Concerns in the OCs and RMMs lead to additional conditions for authorisation presented in section 7, to additional monitoring arrangements presented in section 8 and to recommendations for the review report presented in section 9.

2. Exposure assessment

2.1. Environmental emissions

RAC did not evaluate the predicted environmental concentrations (PECs) provided by the applicant since 4-NPnEO is treated as a non-threshold substance with regard to its endocrine disrupting properties for the environment and therefore no appropriate PNECs are available for comparison, nor is the Water Framework Directive EQS value considered to be suitable for this purpose.

Water

All solid waste and liquid waste from the solvent recovery step is collected for incineration. All process and cleaning water that contain measurable concentrations of emulsifier residues are sent to the carbon filter pre-treatment; only when the level of emulsifier residues in the waste water from the production and cleaning processes are below 1 mg/L, the waste water is directly (i.e. with no carbon filter pre-treatment) released to the on-site WWTP and eventually to the municipal sewage system. Therefore the environmental exposure assessment presented by the applicant is based on these residual releases.

[11] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[12] 'Effectiveness' – evaluation of the degree to which the RMM is successful in producing the desired effect – exposure / emissions reduction, taking into account for example proper installation, maintenance, procedures and relevant training provided.

The applicant noted that the content of 4-NPnEO in liquid process waste and cleaning waters is controlled using two different on-site sampling procedures outlined below:

- To be able to control the content of 4-NPnEO in the waste water from different production units and the degree of purification in the on-site WWTP, the flows are registered, and the sampling is performed using a flow proportionate sampler. The sample preparation is done in a laboratory located at the on-site WWTP. For all collected samples, an extra sample is stored in the freezer in the laboratory until the analysis results have been received.
- During all production weeks, a flow proportional monthly aggregate sample is prepared for the sampling point (samples are taken daily every 30 min) for analysis of various nonylphenols. The monthly sample contains both water and sludge. The monthly aggregate sample is stored in a freezer and when the report month comes to an end the sample is sent to the quality control laboratory for analysis.
- Since January 2016 to measure the quantity of 4-NPnEO coming out of the WWTP, the applicant uses an analytical method based on UHPLC Q-TOF (ultra-high performance liquid chromatography with quadrupole time-of-flight detection) with LOQ of 2 µg/L. The applicant noted that compared to the method originally used, phosphate esters are not included in this analysis, making this method specific to 4-NPnEO and DNPnEO, for n = 2-20. The concentration of 4-NPnEO and DNPnEO in the outgoing effluent is quantified by evaluating chromatographic responses against standard curves.

The applicant estimated the release factor for 2018 based on the mass balance using information on volumes of 4-NPnEO used in 2018 (all volume calculations for usage of 4-NPnEO, are solely based on the 4-NPnEO content purchased and actually used) and releases calculated from measurement results from on-site WWTP for that year[13].

Air

According to the applicant, releases to air are not expected taking into account the activities performed and the low vapour pressure of the substance.

Soil

No direct releases to soil are expected based on the conditions of use of the substance.

[13] Actual calculations are claimed confidential but are made available to RAC.

Table 3: Summary of environmental emissions

Release route	Release factor	Release per year	Release estimation method and details
Water	< 3 %	14.4 kg	Release factor based on mass balance and measured data from 2018 in the waters from on-site WWTP. Applicant's release factor calculation takes into account the 4-NPnEO used in the emulsifiers as well as 4-NPnEO generated from the hydrolysis of the phosphate esters in the emulsifiers, during their use at the site. Projected maximum release per year (i.e. 14.4 kg) is calculated on the basis of the release factor of 2018 and the maximum projected use of 4-NPnEO.

2.2. Discussion of the information provided and any relevant shortcomings or uncertainties related to exposure assessment

Environment

RAC notes that the potential for release is reduced as a result of the use of 4-NPnEO in mainly closed systems and incineration of solid and process liquid wastes. However, there are still residual releases to the local municipal STP due to emulsifier residues in the waste water from the production and cleaning processes. In the CSR the applicant claimed that currently there is an agreement with Uppsala Vatten that nonylphenol emissions should be no greater than 20 kg/year (the permitted amount was lowered from 50 kg/year to 20 kg/year in 2012) and, according to the applicant, during the requested review period the emissions will remain within this limit despite an increase in the production. As a confidential information in the Annex B of the CSR the applicant provided measurement information and release rate estimations for years 2010-2018. RAC notes that the yearly emissions presented by the applicant remained below 20 kg/year since 2011. The applicant considers the maximum value of projected releases to be conservative as it represents the worst-case scenario of failure in the applicant's plans to progressively substitute the use of 4-NPnEO containing emulsifiers.

RAC considers the residual release estimates (up to 14.4 kg/year) to be representative and do not underestimate the total emissions to the environment. RAC points out that the applicant developed its release estimation based on measured data and on volumes of 4-NPnEO purchased and actually used.

Due to the type of production processes and the OCs and RMMs in place, RAC concludes that releases to air are expected to be negligible.

Similarly, RAC agrees that direct releases to soil are not likely. However, RAC notes that indirect releases to soil by means of the use of the municipal STP sludge for agricultural purposes cannot be excluded, as the waste water leaving the site is discharged into a sewer and going to a municipal waste water treatment plant that uses about 50 % of accumulated sludge on agricultural soil.

2.3. Conclusions on exposure assessment

RAC considers that the exposure estimates provided by the applicant are appropriate. RAC did not identify shortcomings in the methodology used that would invalidate this conclusion.

3. Risk characterisation

3.1. Environment

The applicant has treated 4-NPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with RAC's paper "Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO" adopted at RAC-43.

The use applied for may result in up to 14.4 kg/year emissions of 4-NPnEO to the environment due to emulsifier residues in the waste water from the production and cleaning processes. With regard to future release estimates (covering the requested review period), taking into account maximum use and maximum release projected by the applicant, RAC points out that the maximum release to the municipal STP (i.e. 14.4 kg/year) represents about threefold increase compared to the situation in 2018 but will still stay below the maximum amount permitted (< 20 kg/year), as per the agreement with Uppsala Vatten. RAC acknowledges that the maximum releases are only envisioned as the worst-case scenario if the applicant's plan to progressively substitute the use of 4-NPnEO containing emulsifiers fail. In the answers to RAC questions the applicant noted that currently the substitution process is proceeding successfully and the applicant is planning to reduce the use and releases of 4-NPnEO containing emulsifiers starting from 2022. Nevertheless, RAC is of the opinion that a worst-case scenario of a threefold increase in the emissions when the maximum tonnage is used is a cause for concern. Thus, RAC is of the view that emissions to the water compartment should be minimised by implementing additional OCs and RMMs.

3.2. Shortcomings or uncertainties in the risk characterisation

No significant shortcomings were identified in the risk characterisation.

3.3. Conclusions on risk characterisation

Based on the OCs and RMMs in the exposure scenario, RAC is of the view that the applicant has not demonstrated that its releases of 4-NPnEO to the environment due to emulsifier residues in the waste water from the production and cleaning processes have been prevented or minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

4. Analysis of Alternatives and substitution plan[14]

What is the amount of substance that the applicant uses per year for the use applied for?

< 1 tonne/year

4.1. Summary of the Analysis of Alternatives and substitution plan by the applicant and of the comments received during the consultation and other information available

In its analysis of alternatives, the applicant considered both alternative substances, i.e. alternative emulsifiers, and alternative technologies. The applicant's substitution efforts are however focused on alternative emulsifiers as the aim is to develop and implement a one-to-one alternative to the currently used emulsifiers containing 4-NPnEO. According to the applicant, robust and reliable product quality of the chromatography resins it supplies has to be guaranteed, particularly for the resins used in the industrial manufacturing process of biological APIs where the quality, purity and efficacy of the purified biomolecule must be ensured. As such an alternative emulsifier must meet all of the following key functionalities before it can be considered for further development, testing and scale-up:

- **Solvent phase preparation**: To become solubilized in hot solvent solution phase.
- **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).
- **Emulsification efficiency**: To facilitate the droplet size reduction emulsification process to reach targeted drop size distribution.
- **Stabilization (particle formation)**: To stabilize droplet during cooling and particle formation to minimize particle defects (stabilization of droplets-particles).
- **Washing**: To be removed from base matrix resin; low interference of emulsifier residues with process conditions.
- **Other**: Other ways by which the emulsifier substance influence process and product quality.

In 2003 the applicant initiated an R&D programme to identify an alternative emulsifier that could replace the emulsifiers containing 4-NPnEO in the manufacturing of the intermediate resins using current manufacturing technology. Based on literature research the applicant screened more than 100 commercially available emulsifiers (full list provided in Annex A of the AoA/SEA). Subsequently, this initial list of potential alternative emulsifiers was narrowed down taking into account a number of criteria, including performance with respect to emulsification efficiency and stabilization, chemical structure, previous experience with the identified substances, environmental properties, supply aspects and potential for implementation in a large part of the product portfolio. In response to a SEAC question, the applicant explained that this last criterion enables both radical simplification of implemented use and potential for reduced implementation time for the whole substitution program. In the end the applicant

[14] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be "*in abstracto*" or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

selected six emulsifiers for further evaluation from this stream of work.

In addition, in 2016 the applicant commissioned an external research institution, SP RISE (Technical Research Institute of Sweden), to screen and identify potential alternative emulsifiers. SP RISE identified 82 candidate emulsifiers which the applicant narrowed down to six emulsifiers, either on the basis of previous experience from the in-house R&D programme, or because of poor test results or structural similarity to candidates that had shown poor test results, or due to structural similarity with the six emulsifiers already identified in the in-house screening activities.

The applicant's in-house screening activities and the external screening by SP RISE together with suggestions from suppliers led to identification of 25 candidate emulsifiers (14 phosphate ester emulsifiers and 11 non-ionic emulsifiers) for further evaluation. Following further lab scale testing of these 25 emulsifiers, the four most promising potential alternatives belonging to the group of phosphate ester emulsifiers have been short-listed by the applicant. The short-listed alternatives have been claimed confidential by the applicant and are referred to as Alternative Emulsifier A, B, C and D. Two of the short-listed alternatives have been prioritized by the applicant for further feasibility testing.

Apart from alternative emulsifiers, the applicant also considered alternative technologies for the manufacture of the intermediate resins. According to the applicant, its current manufacturing technology, based on an emulsion templating route for porous polymer particles, represents the only established technology for the manufacturing of chromatography resins based on agarose, which make up the large majority of the applicant's product portfolio that uses emulsifiers containing 4-NPnEO. The applicant considers the technical feasibility to develop an alternative particle manufacturing method that is not based on an emulsion template approach as low, given that the alternative process technology must lead to end products that are interchangeable in the user applications (e.g. for biopharmaceutical purification).

No additional information on alternatives has been received during the consultation.

SEAC notes that the applicant considered both alternative substances and alternative technologies and explained why its substitution efforts are focused on identifying suitable alternative emulsifiers. Taking into account the information provided in the application together with the additional clarifications provided by the applicant, SEAC finds that the approach to identify potential alternatives appears comprehensive and is clearly described. SEAC notes that the applicant clearly set out the functional requirements a proposed alternative would have to meet and provided information on the technical limitations observed for the rejected alternatives. SEAC further notes that the applicant provided information on the technical and economic feasibility and availability of the two short-listed alternatives that have been prioritized for further feasibility testing. SEAC considers the information provided as sufficient for concluding on the validity of the assessment.

4.2. Risk reduction capacity of the alternatives

Would the implementation of the short-listed alternative(s) lead to an overall reduction of risks?

☐Yes

☐No

☒Not applicable

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

4.3. Availability and technical and economic feasibility of alternatives for the applicant

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

All four short-listed alternatives are phosphate ester emulsifiers which, according to the applicant, are structurally similar to the currently used emulsifiers containing 4-NPnEO. The applicant expects the similar structure of the short-listed alternative emulsifiers to require only minor process modifications.

Two of the four short-listed alternatives, Alternative Emulsifier A and Alternative Emulsifier D, have been prioritised by the applicant for further laboratory and pilot testing to assess their technical feasibility. The prioritisation was done based on the key functionalities described in Section 4.1 above and its outcome is reported in Annex B of the AoA/SEA. Even though the prioritisation exercise ranked Alternative Emulsifier C as the top candidate, further discussions with the supplier of this alternative led the applicant to deprioritise it. In response to a SEAC question the applicant explained that on the basis of supplier site audits and in-depth discussions it became apparent that both manufacturing flexibility and specification details were unfavourable for Alternative Emulsifier C in comparison to Alternative Emulsifier D. Alternative Emulsifier C was deprioritised because it can only be produced at one supplier site and because its specifications allow significant product quality variations.

For the two prioritised alternatives, Alternative Emulsifier A and Alternative Emulsifier D, the applicant provided further information on technical and economic feasibility as well as availability.

The applicant has performed lab scale process adaptation studies to assess the technical feasibility of Alternative Emulsifier A and Alternative Emulsifier D. According to the applicant, these preliminary R&D studies indicate that both emulsifiers are promising alternatives to the currently used 4-NPnEO containing emulsifiers and that their implementation would only require minor process modifications. The applicant stated however that currently neither of the two alternatives can be considered technically feasible as additional studies are required to address some remaining issues that have been identified during preliminary R&D studies. These issues are related to differences in the by-product impurity pattern compared to the currently used 4-NPnEO containing emulsifiers.

The applicant stated that, following the laboratory and pilot scale testing to identify a technically feasible alternative, further R&D activities are required for the adaptation of the current process and reaction conditions to such an alternative emulsifier. These activities are common to all 13 intermediate resin products currently relying on emulsifiers that contain 4-NPnEO and need to be carried out only once, assuming that the chosen alternative is applicable for all 13 affected products. However, according to the applicant, a series of additional activities are needed for the implementation of an alternative emulsifier, which have to be completed for each of the 13 affected products in a sequential manner. These activities include: development of characterisation methods and product baseline; development of production

base methods; installation of manufacturing equipment; technical trials and process verification; process validation; and customer notifications. The applicant expects that all necessary activities for the first product will be completed in 2021, with substitution activities for the other 12 products to follow thereafter.

Regarding economic feasibility, the applicant stated that the costs for Alternative Emulsifier A would be comparable to the costs for the currently used 4-NPnEO containing emulsifiers. The applicant also expects Alternative Emulsifier A to be available in sufficient quantities even though the specific product chemistry of the alternative is only available from one chemical supplier. The applicant made some considerations on the economic feasibility of Alternative Emulsifier D, though these were claimed confidential. The applicant stated that the specific product chemistry of Alternative Emulsifier D is only available from one chemical supplier but that it is available in sufficient quantities.

SEAC's evaluation/view on the availability and technical and economic feasibility of alternatives for the applicant

SEAC agrees with the applicant's conclusion that no technically feasible alternatives to the use applied for are available before the sunset date. The assessed alternatives are still under development and more time will be needed for research and testing. Once the technical feasibility of an alternative emulsifier has been confirmed at lab and pilot scale, additional steps are needed for process adaptation and for implementation of the alternative emulsifier in the manufacturing of all 13 intermediate resins which currently rely on 4-NPnEO containing emulsifiers.

4.4. Substitution activities/plan

Has the applicant submitted a substitution plan?

☒Yes ☐No

If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

At the time of submitting its application, the applicant understood that the submission of a substitution plan within the application was required only when a suitable alternative is available to the applicant. In light of the judgment of the ECJ Case-T-837/16, ECHA invited the applicant to consider the submission of a substitution plan. This plan was therefore submitted by the applicant in response to ECHA's invitation.

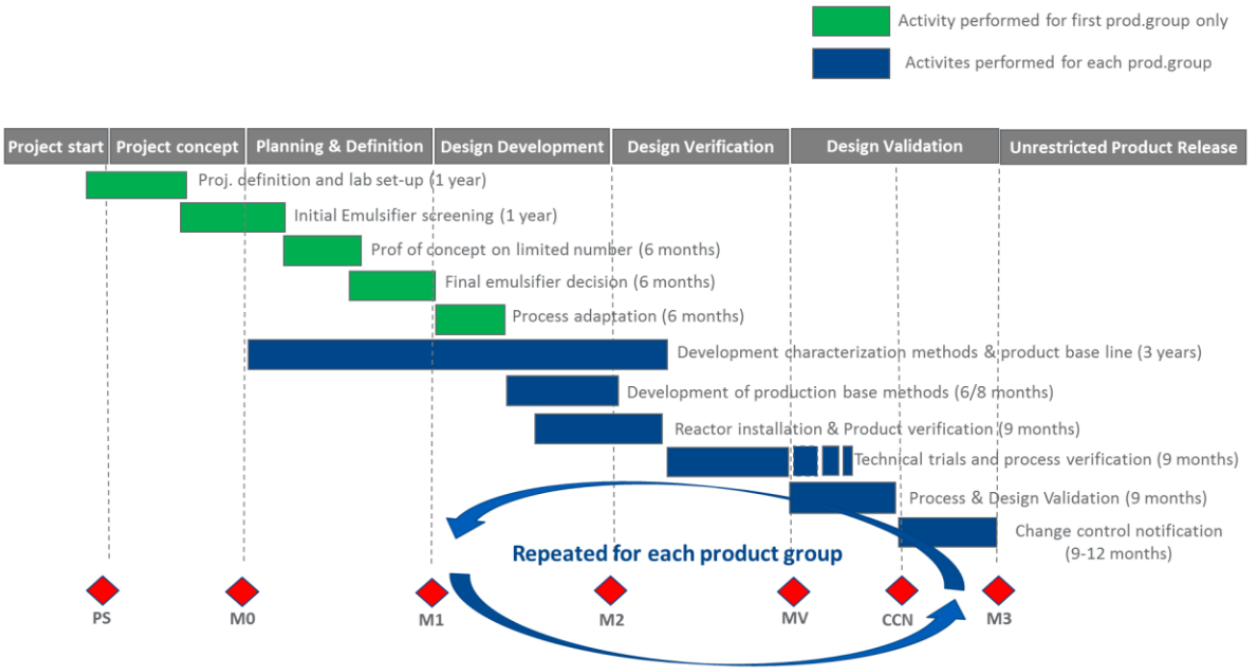
SEAC notes that the majority of the information contained in the substitution plan was already reflected in the original application. SEAC takes note, however, of the additional information on the monitoring of the implementation of the substitution plan.

The applicant is engaged in a substitution programme and R&D activities have already been carried out since 2003. So far the applicant has not been able to identify a suitable alternative to replace the 4-NPnEO containing emulsifiers used in the manufacturing of the 13 intermediate resins. However, the applicant has identified two promising potential alternatives and outlined the activities and timelines required to achieve full substitution of 4-NPnEO.

The activities to be carried out for each of the 13 affected intermediate resins (referred to as "product groups" by the applicant) together with their estimated duration are shown in Figure 1. The activities in green are common to all product groups and only need to be carried once,

assuming that the chosen alternative is applicable for all 13 affected intermediate resin products. The activities in blue need to be carried out for all product groups.

Figure 1: Substitution activities performed per product group



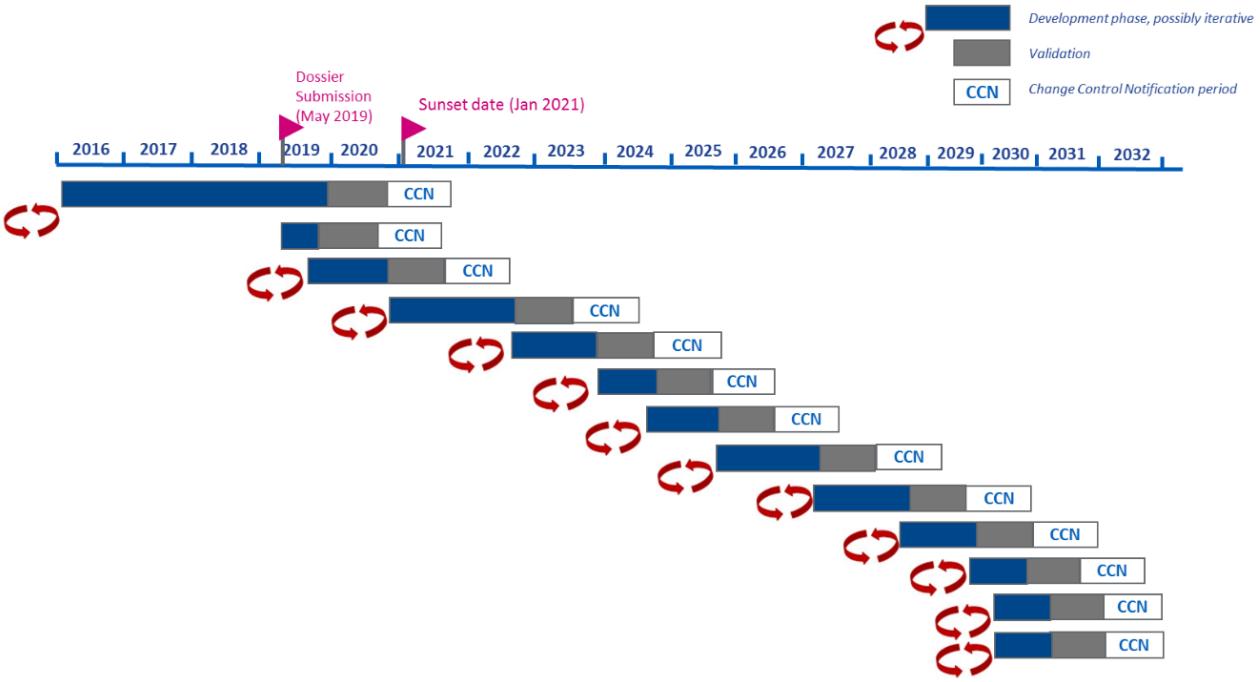
SEAC asked the applicant to provide further information on the presented substitution activities and their duration, in particular for the activity with the longest duration, i.e. the development of characterisation methods and product baseline. The applicant explained that to ensure the quality of the intermediate resin products and consequently the chromatography resin end products after implementing an alternative emulsifier, existing test methods have to be modified or new test methods have to be developed for the characterisation of samples produced using an alternative. The applicant further noted that, following the development of these methods, a dataset has to be established on tested production samples which can be used as a reference ("product baseline") for quality control purposes. Furthermore, the applicant stated that methods for the quantification of an alternative emulsifier need to be developed.

The applicant also explained that the intention of Figure 1 was to display the various activities required in the substitution process and their approximate duration but that the timelines for the various tasks will vary across the 13 product groups. According to the applicant this is because experiences from product groups where substitution will take place earlier can be applied to subsequent groups and because the number of chromatography resin end products eventually manufactured from the intermediate resins differs between product groups.

Based on the activities required for implementing an alternative in all 13 affected intermediate resin products, the applicant foresees a period of 12 years from the sunset date to attain full substitution and therefore requested a 12-year review period. Substitution of the 4-NPnEO containing emulsifiers will be carried out in a staggered manner for the 13 product groups as shown in Figure 2. The priority for substitution was set according to the quantity of emulsifiers containing 4-NPnEO used in the production of each product group. The applicant expects that all necessary activities for the first product group will be completed in 2021, with substitution activities for the other 12 groups to follow thereafter. The applicant justified the staggered approach from an economic perspective because laboratory investigations are complex and

require a considerable amount of time and resources and from a technical perspective because of limited access to manufacturing equipment which continues to be used to manufacture intermediate resins (depending on 4-NPnEO containing emulsifiers and others) to meet market demand.

Figure 2: Staggered substitution approach



With regard to the monitoring of the substitution plan's implementation, the applicant stated that changes in manufacturing processes, including the substitution of 4-NPnEO containing emulsifiers, are managed in accordance with its Change Control Process for Designated Products. Each manufacturing unit has a change control review board headed by quality assurance (QA) with representatives from QA, manufacturing and other relevant functions. Due to its complexities, the substitution project is run within the R&D department and follows the applicant's Quality Management System and the standard framework for project monitoring and decision making. Project progress is monitored in monthly status reports and deviations from planned or agreed timelines or costs require follow-up and new formal approvals by the project review committee.

SEAC's evaluation/view on the substitution activities/plan

SEAC finds the presented substitution plan and the described substitution activities and R&D credible, including the description of the main steps to be completed, the expected outcome of each main step and the timelines for completion assigned to each of them. SEAC finds credible the economic and technical arguments given by the applicant to justify that substitution of 4-NPnEO containing emulsifiers used in the manufacturing of the 13 intermediate resins can only happen in a staggered manner. As such, SEAC finds credible the applicant's conclusion that the activities required to attain full substitution across the entire range of products would require the requested review period.

4.5. Conclusions on the analysis of alternatives and the substitution plan

By the sunset date there are no alternatives available with the same function and similar level

of performance that are safer and technically and/or economically feasible for the applicant. The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

5. Benefits and risks of continued use

Has the applicant adequately assessed the benefits and the risks of continued use?

☒ Yes

☐ No

5.1. Human health and environmental impacts of continued use

According to the applicant, releases of 4-NPnEO to the environment are effectively minimised and limited to residual 4-NPnEO remaining in the waste water following pre-treatment with active carbon. Discharges from the applicant's on-site waste water treatment plant reach the municipal STP and are ultimately released to the Fyris River. The 80 km long Fyris River has a 2 000 km^2 catchment area and flows into Lake Ekoln, a northern part of Lake Malaren, which flows into the Baltic Sea. Other waste that has been in contact with 4-NPnEO containing emulsifiers – consisting of emptied barrels, containers, cans, funnels, gloves and other personal protective equipment – is collected and disposed of as hazardous waste through incineration by a licensed contractor.

The applicant estimated releases of 4-NPnEO to the environment of up to 14.4 kg/year, which corresponds to releases of up to 173 kg over 12 years. The estimated releases are considered conservative by the applicant because they are calculated on an annual tonnage of 4-NPnEO containing emulsifiers (< 1 tonne/year; non-confidential range) that takes into account potential future sales growth and the worst-case scenario of failure in the plans to progressively substitute the use of 4-NPnEO containing emulsifiers.

The applicant has attempted to monetise the environmental impacts from the use applied for based on a study by the Vrije Universiteit Amsterdam (VU, 2015) assessing the costs of reducing releases of PBT/vPvB substances[15]. The VU study collected information on costs to reduce the stocks, presence, flows and emissions to the environment of PBT substances and, where possible, related this information to whether the reduction measure had been implemented or rejected due to those costs. Based on the assessment, VU suggested that there is a "grey zone" of €1 000-50 000/kg in which the measures to reduce the use, presence or emission of PBTs may be prohibitive from a cost-effectiveness point of view.

Based on the €/kg ranges from the VU study and the estimated emissions of 173 kg over the requested review period, the applicant provided an upper and a lower bound of monetised environmental impacts of continued use (values claimed confidential). SEAC takes note of this monetised impact but does not consider it relevant for any cost-benefit analysis, since the costs related to reducing PBT/vPvB substances cannot be directly applied to substances with endocrine disrupting properties for the environment and since the €/kg range derived in the VU (2015) study cannot be interpreted as social costs of 4-tert-OPnEO emissions.

In response to a question by the Committees, the applicant claimed not to be aware of another treatment technology that would allow it to eliminate 4-NPnEO emissions further to the current

[15] Oosterhuis, F. and Brouwer, R. Benchmark development for the proportionality assessment of PBT and vPvB substances. Amsterdam: IVM Institute for Environmental Studies - University Amsterdam, 2015.

99 % abatement rate provided by the implemented active carbon pre-treatment. The applicant also claimed that a further reduction of 4-NPnEO emissions would require the active carbon pre-treatment for the large volume of effluents with 4-NPnEO residues below the detection limit, which would require additional investments to increase the carbon filter capacity. Another possibility would be to invest in an in-house sludge separation facility. The applicant claimed that these types of investments would take at least 5 years to implement with associated investment costs in the order of tens of millions of euros[16], based on previous experience. According to the applicant, such an investment is not considered cost-effective given the limited time until substitution is completed.

Human health impacts of continued use are not assessed as 4-NPnEO is listed on Annex XIV of REACH for its endocrine disrupting properties for the environment.

5.2. Benefits of continued use

Non-use scenario

The applicant has considered different non-use scenarios (substitution, temporary shutdown, permanent shutdown with or without relocation outside the EEA). After ruling out substitution, given the conclusion that no suitable alternative is available before the sunset date, the applicant also discarded the option to shut down the production lines which are currently manufacturing chromatography resins dependent on 4-NPnEO without relocation, because of the substantial financial impacts to the applicant (including also the loss of reputation and possible commercial penalties) and long-term impacts to the biopharmaceutical industry and its patients and the food sector. The applicant carried out a comparative cost assessment (details claimed confidential) of the two remaining scenarios (permanent shutdown with relocation of production outside the EEA and temporary shutdown until substitution is completed) and concluded that the least expensive and therefore most plausible scenario is the temporary production shutdown of the more than 120 chromatography resin end products depending on the 13 intermediate resins which are manufactured using 4-NPnEO containing emulsifiers.

What is likely to happen to the use of the substance if an authorisation was not granted?

- the use would cease altogether
- the use would be substituted by market actors operating inside the EU
- the use would be taken up by market actors operating outside the EU

What is likely to happen to jobs in the European Union if an authorisation was refused?

- 10-100 jobs would be lost

[16] Actual investment costs are claimed confidential but are known to SEAC.

Socio-economic impacts of continued use

In the applicant's most likely non-use scenario there would by a temporary supply chain disruption of the more than 120 affected chromatography resin end products. This would impact the applicant, its customers (biopharmaceutical manufacturers) and patients. The applicant stated the main impacts of the non-use scenario as follows:

- **Economic impacts on applicant**: The applicant stated that a temporary shutdown would mean economic impacts in the form of lost profits related to the sales of chromatography resin end products which depend on the intermediate resins manufactured using 4-NPnEO containing emulsifiers. The applicant provided a non-confidential range of the estimated profit losses of €500-1 500 million (in present value terms, discounted at 4 %) over the 2021-2032 period, i.e. over the 12-year review period applied for. SEAC considers that changes in profits are a relevant measure of changes in producer surplus and appropriate to monetise the welfare implications of continued use. However, changes in profits made by the applicant do not necessarily reflect net changes in economic surplus across the EU economy. Considering the profit losses of the applicant over a long time period does not take into account the possibility of mitigating actions that could reduce the economic impacts (e.g. resources being redeployed by the applicant or by other companies) and may overstate the long-term impacts. Considering only one year of profit losses would still imply economic impacts of around €42-125 million (calculated as €500-€1 500 million divided by the length of the assessment period, i.e. 12 years). This value is taken forward by SEAC for the cost-effectiveness analysis.
- **Economic impacts on biopharmaceutical manufacturers**: The applicant described potentially dramatic economic consequences for manufacturers of biological APIs using the affected chromatography resins. According to the applicant more than 70 biopharmaceutical manufacturers use the affected chromatography resins in the manufacturing processes of at least 190 approved and registered biological APIs. In the non-use scenario these companies would have to discontinue, suspend or completely redesign the manufacturing process of the concerned biological APIs. The applicant stated that any of these options would result in severe economic impacts on the biopharmaceutical manufacturers, including revenue losses (stated as €130 billion per year but no further substantiation provided by the applicant), penalties and reputational damage.
- **Impacts on patients**: The applicant stated that at least 190 human therapeutics and vaccines for various diseases, including life-threatening diseases, would no longer be available on the global market. The applicant acknowledged that some of these human therapeutics and vaccines might be available from other biopharmaceutical companies not using the applicant's affected chromatography resins but stated that the non-use scenario would still create a shortage in the availability of some medicines.
- **Social impacts related to unemployment**: The applicant estimated that in the non-use scenario the equivalent of 10-100 directly associated jobs (non-confidential range) would be lost resulting in social costs of €1-11 million. Accounting also for indirectly associated jobs, the applicant estimated that 100-500 (non-confidential range) jobs would be lost resulting in social costs of €11-50 million. In estimating the social costs of unemployment the applicant followed the methodology outlined in Dubourg (2016)[17] and endorsed by SEAC (2016)[18]. In order to be conservative, SEAC takes forward the

[17] Dubourg (2016): https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554
[18] SEAC (2016):

value related to the loss of directly associated jobs, i.e. €1-11 million, for the cost-effectiveness analysis.

- **Reduction of R&D investments**: The applicant explained that overall R&D investments would decrease as the profitability of its manufacturing site would be impacted in the non-use scenario. As a result several new product introductions, which are considered enablers for the applicant's biopharma customers, would be missed with potentially far-reaching wider socio-economic impacts.

Table 4: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts (over the 12-year assessment period)
1. Benefits to the applicant and/or their supply chain	
1.1 Avoided profit loss due to investment and/or production costs related to the adoption of an alternative	Not relevant
1.2 Avoided profit loss due to ceasing the use applied for[1]	€42-125 million
1.3 Avoided relocation or closure cost	Not relevant
1.4 Avoided residual value of capital	Not relevant
1.5 Avoided additional cost for transportation, quality testing, etc.	Not relevant
Sum of benefits to the applicant and/or their supply chain	*€42-125 million*
2. Quantified impacts of the continuation of the SVHC use applied for on other actors	
2.1 Avoided net job loss in the affected industry[2]	€1-11 million
2.2 Foregone spill-over impact on surplus of alternative producers	Not quantified
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	Not quantified
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	Not quantified
Sum of impacts of continuation of the use applied for	*€1-11 million*
3. Aggregated socio-economic benefits (1+2)	**€43-136 million**

Notes:

1. SEAC considered one year of profit loss only as explained under *Economic impacts on applicant* in Section 5.2 above.
2. SEAC considered the value related to the loss of directly associated jobs only as explained under *Social impacts related to unemployment* in Section 5.2 above.

5.3. Combined assessment of impacts

For the quantitative comparison of impacts, SEAC considers monetised benefits of continued use of €43-136 million over the 12-year assessment period, consisting of one year of lost profits (€42-125 million) and the applicant's more conservative estimate of the social costs of unemployment (€1-11 million), as explained in Section 5.2. On the other hand, the applicant estimated that, over the 12-year assessment period, up to 173 kg of 4-NPnEO releases to the environment could be avoided in the non-use scenario. This gives a cost-effectiveness ratio of

https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25

€0.2-0.8 million per kg of 4-NPnEO releases avoided.

Even though the cost-effectiveness ratio only considers the monetised benefits of continued use, SEAC also takes note of the other relevant benefits of continued use described qualitatively by the applicant, in particular economic impacts on biopharmaceutical manufacturers and impacts on patients.

Table 5: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€43-136 million (over the 12-year assessment period)	Monetised excess risks to workers directly exposed in the use applied for	Not relevant
Quantified impacts of the continuation of the SVHC use applied for	Not quantified	Monetised excess risks to the general population and indirectly exposed workers	Not relevant
Additional qualitatively assessed impacts	Avoided economic impacts (revenue losses, penalties, reputational damage) on > 70 biopharmaceutical manufacturers using the affected chromatography resins Avoided impacts on patients due to unavailability of > 190 human therapeutics and vaccines Avoided wider socio-economic impacts due to applicant's reduction of R&D investments	Additional qualitatively assessed risks	Environmental impacts associated with releases of 4-NPnEO of up to 173 kg (over the 12-year assessment period)
Summary of socio-economic benefits	**Aggregated socio-economic benefits: €43-136 million (over the 12-year assessment period)** **Avoided economic impacts on biopharmaceutical manufacturers, avoided impacts on patients, avoided wider socio-economic impacts**	**Summary of excess risk**	**Environmental impacts associated with releases of 4-NPnEO of up to 173 kg (over the 12-year assessment period)**

Table 6: Cost of non-use per kg

	Over the 12-year assessment period
Total cost[1] (€)	€43-136 million
Total emissions[2] (kg of 4-NPnEO)	173 kg
Ratio[3] (€/kg of 4-NPnEO)	€0.2-0.8 million/kg of 4-NPnEO

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg over the 12-year assessment period, based on Table 3
3. "Ratio" = Total cost/Total emissions

5.4. SEAC's view on Socio-economic analysis

SEAC reviewed the comparative assessment of four possible non-use scenarios carried out by the applicant and finds overall that the analysis is transparent and justifies that the chosen non-use scenario is the most likely, given that it is the least expensive to the applicant and therefore the most economically credible. The applicant indicated that it would incur substantial financial impacts and significant impacts in terms of commercial penalties and loss of reputation under both preferred non-use scenarios (temporary shutdown, permanent shutdown with relocation outside the EEA) in relation to the interruption of supply. The applicant did not compare the relative importance of these impacts in the two preferred non-use scenarios but it is plausible that they would be of relatively similar importance. In case of a temporary shutdown, the staggered substitution approach implies that resumption of production will also be staggered and therefore could generate less impacts than a permanent shutdown and relocation outside the EEA.

SEAC agrees with the applicant's analysis that non-use would entail significant economic impacts and finds that the costs of the non-use scenario (i.e. benefits of continued use) presented provide an acceptable estimate of these costs. It should however be noted that mitigating actions that could reduce the economic impacts (e.g. resources being redeployed by the applicant or by other companies) were not enough considered. SEAC therefore recalculated the economic impacts on the applicant considering only one year of profit losses but notes that adopting such an approach does not change the conclusions on the appropriateness of the applicant's assessment.

SEAC is also conscious of the potential impacts on the supply of biopharmaceuticals and consequences on biopharmaceutical manufacturers and public health in the EU. SEAC finds that these impacts are difficult to assess but agrees they are potentially very significant. SEAC asked the applicant to provide an indication of the number of patients that are treated with medicines that are manufactured using the applicant's chromatography resins depending on intermediate resins made with 4-NPnEO containing emulsifiers. The applicant explained that such an estimate is very difficult to make but nevertheless provided an order of magnitude estimate of 200 million patients. Since the applicant might not be the only manufacturer of chromatography resins for the manufacturing of biopharmaceuticals, this might be an overestimate of the number of patients depending on this application, but it confirms the magnitude of potential impacts.

SEAC agrees with the applicant's calculations of the number and social costs of lost jobs in case authorisation is not granted. The applicant followed the methodology endorsed by SEAC for valuing of the social costs of job losses and SEAC has no reservations on the way this methodology has been applied.

Overall, SEAC considers that the socio-economic analysis presented by the applicant is a credible basis to address benefits and costs of granting the authorisation.

5.5. Conclusion on the socio-economic analysis

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- SEAC's assessment of the availability, technical and economic feasibility of alternatives,
- additional information provided by the applicant,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. years)

☐ Other: _____ years

When recommending the review period SEAC took note of the following considerations:

6.1. RAC's advice

RAC gives no advice on the length of the review period.

6.2. Substitution and socio-economic considerations

The applicant requested a 12-year review period for the development, implementation and validation of alternatives to 4-NPnEO containing emulsifiers. The applicant estimated the length of the individual stages needed to carry out the substitution process and noted that the resulting total duration for achieving full substitution is aligned with the requested review period. The applicant justified the requested review period also by economic and technical arguments due to which substitution of 4-NPnEO containing emulsifiers can only happen in a staggered manner across the 13 affected intermediate resins.

SEAC considered that:

- It does not appear possible to carry out full substitution for all product groups within a normal review period.
- The economic and technical arguments given by the applicant to justify the staggered substitution approach across the 13 affected intermediate resins appear credible.
- In the context of the pharmaceutical industry there are certification constraints that can justify a long review period.

- There are indications that the benefits of continued use are high in terms of public health with continued full provision of critical medicines and vaccines in the EU and this situation is not likely to change in the next decade.

Taking into account these points, SEAC recommends a **12**-year review period.

7. Proposed additional conditions for the authorisation

Were additional conditions[19] proposed for the authorisation?

☒ Yes

☐ No

7.1. Description

RAC

Proposed additional conditions

All emissions of 4-NPnEO to the environment shall be subject to adequate treatment with the view of minimisation of releases to the environment.

The applicant shall conduct a mass balance calculation annually. The results shall include details of the calculations carried out, any assumptions made and the corresponding environmental release values. The information gained that way should be made available to National Enforcement Authorities upon request.

SEAC

Proposed additional conditions

Not relevant.

7.2. Justification

Release into the municipal sewer system or to surface waters cannot be considered as adequate treatment. Thus, RAC is of the opinion that untreated releases of wastewater containing 4-NPnEO to the water compartment should be minimised by implementing additional OCs and RMMs.

The annual calculation of a mass balance should allow the evaluation of the effectiveness of the new additional and already existing OCs and RMMs in place and to confirm that emissions are reduced to as low a level as is technically and practically possible.

[19] Conditions are to be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[20] proposed for the authorisation?

☒ Yes

☐ No

8.1. Description

The applicant should continue to monitor at least quarterly/four times per year (during the time of operation) the concentration and total amount of 4-NPnEO and its principal degradation products in the waste water prior to release to the off-site municipal STP using an analytical method capable of adequately characterising the substance and its principal degradation products in water at an appropriately low level of quantification.

8.2. Justification

The measurement results provided at least quarterly/four times per year (during the time of operation) should allow the evaluation of the effectiveness of the new additional and already existing OCs and RMMs in place and to confirm that emissions are reduced to as low a level as it is technically and practically possible. The frequency of the measurements should be sufficient to capture the variability in concentrations of the substance and its degradation products in the waste water (e.g. due to changes or operational fluctuations in the process).

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1. Description

The results of the monitoring programme referred to in section 8.1 should be included in any review report, including details of sampling point, the analytical method, the concentrations detected and the corresponding environmental release values. Furthermore, the outcome and conclusions of the actions taken following the conditions in section 7.1, shall be documented and included in any subsequent authorisation review report.

9.2. Justifications

The measurement results provided at least quarterly/four times per year (during the time of operation) should allow the evaluation of the effectiveness of the additional OCs and RMMs in place and to confirm that emissions are reduced to as low a level as is technically and practically possible.

[20] Monitoring arrangements for the authorisation are to be proposed where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but there are some moderate concerns.

10. Comments on the draft final opinion

Did the applicant provide comments on the draft final opinion?

☐ Yes

☒ No

Comments of the applicant

Was action taken resulting from the analysis of the comments of the applicant?

☐ Yes

☐ No

☒ Not applicable – the applicant did not comment

Reasons for introducing the changes and changes made to the opinion

Not applicable – the applicant did not comment.

Reasons for not amending the opinion

Not applicable – the applicant did not comment.