Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO)

Use of 4-tert-OPnEO as Triton X-100 as detergent for virus inactivation in the manufacturing process of the human plasma-derived medicinal products Plasmagrade/Plasmasafe and Resusix, as well as Plasminogen (pre-commercialization name) and any subsequent commercialization brand

Submitting applicant

Kedrion S.p.A

ECHA/RAC/SEAC: AFA-O-0000006746-64-01/D

Consolidated version

Date: 20/05/2020

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	**Kedrion S.p.A** (position in supply chain: downstream)
Substance ID EC No CAS No	**4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (in what follows referred to as 4-tert-OPnEO)** - -
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	**Use of 4-tert-OPnEO as Triton X-100 as detergent for virus inactivation in the manufacturing process of the human plasma-derived medicinal products Plasmagrade/Plasmasafe and Resusix, as well as Plasminogen (pre-commercialization name) and any subsequent commercialization brand**
	Other connected uses: Not applicable
	Similar uses applied for: 0170-01, 0176-01, 0178-01
Use performed by	☒ Applicant ☐ Downstream User(s) of the applicant
Use ID (ECHA website)	0155-01
Reference number	11-2120816833-53-0001

RAC Rapporteur	DUNAUSKIENĖ Lina
SEAC Rapporteur SEAC Co-rapporteur	BRIGNON Jean-Marc DOMINIAK Dorota
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PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	17/05/2019
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/23823/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) 23/10/2019 (RAC) Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23823/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	Not held – Not needed considering no new information submitted in 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: 30/03/2020, 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)	20/05/2020
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: 20/05/2020, adopted by consensus.
	SEAC: 20/05/2020, 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 appropriate and effective in limiting the risk, provided that they are adhered to.

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

The use applied for may result in emissions of the substance to the environment of up to 2.5 kg per year in 2021 with a maximum expected release of 5 kg per year in 2035.

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):

- Tween 80 (polyoxyethylene (80) sorbitan monooleate)
- TDAO (N,N-dimethyltetradecylamine N-oxide)
- Nereid

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 €33.5 million (over the 15-year assessment period) and additional benefits to society have been assessed qualitatively but have not been monetised. These additional benefits comprise, in particular, the avoided negative impacts on hospitals and patients related to the unavailability of Plasmagrade/Plasmasafe, Resusix and Plasminogen.
- 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

SEAC considered that, if an authorisation was refused, it was likely that in the European Union:[1]

- 69 jobs would be lost

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

No conditions for the authorisation or monitoring arrangements for the authorisation are proposed.

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.

[1] 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 Sant' Antimo, Italy
Annual tonnage of Annex XIV substance used per site (or total for all sites)	0.5-1 tonne/year
Function(s) of the Annex XIV substance	4-tert-OPnEO is used by the applicant to inactivate lipid-enveloped viruses. The polar head group of 4-tert-OPnEO disrupts the hydrogen bonds between lipid molecules in the lipid bilayer of the virus causing this to decay. In addition, 4-tert-OPnEO helps to stabilise the organic solvent, Tri(n-butyl)phosphate (TNBP), used in the solvent/detergent (S/D) treatment. When the lipid bilayer decays, the viral genome is exposed and can be destroyed by enzymes (nucleases) that are naturally present in blood (and in plasma).
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	4-tert-OPnEO is used in the manufacturing process of three human plasma-derived medicinal products: Plasmagrade/Plasmasafe, Resusix and Plasminogen. Out of these products, only Plasmagrade/Plasmasafe is currently available on the market whereas Resusix and Plasminogen are still in the clinical study phase and pre-registration, respectively.
Shortlisted alternatives discussed in the application	Alternative substances considered: • Tween 80 (polyoxyethylene (80) sorbitan monooleate) • TDAO (N,N-dimethyltetradecylamine N-oxide) • Nereid
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 exposure/release used by applicant for risk characterisation	Environment: • Water: 2.5 kg/year (2021) to 5 kg/year (2035) based on a release factor of 0.5 % (mass balance) • Air: 0 kg/year (emissions to air are considered negligible due to the absence of elevated temperatures during the process and low vapour pressure of 4-tert-OPnEO) • Soil: 0 kg/year (direct release to soil is considered negligible)
Risk Characterisation	Environmental compartments: The applicant has treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. The CSR describes how the operational conditions (OCs) and risk management measures (RMMs) in the exposure scenario prevent or minimise releases to the environment as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).
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)	15 years
Most likely Non-Use scenario	Cessation of production of the three human plasma-derived medicinal products

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: €20 million (over the 15-year assessment period)
Society's benefits of continued use As reported by the applicant	Avoided job loss: €13.5 million (over the 15-year assessment period) Impacts on hospitals and patients related to unavailability of Plasmagrade/Plasmasafe, Resusix and Plasminogen Other social or wider economic impacts on the Italian healthcare system and related to reputational damage
Distributional impacts if authorisation is not granted As reported by the applicant	Possible gains for manufacturers of competitive products while other stakeholders or socio-economic groups (including suppliers, hospitals and patients) would suffer
Job loss impacts if authorisation is not granted	69

SUMMARY OF RAC AND SEAC CONCLUSIONS[2]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

Since all solid waste, which has been in contact with 4-tert-OPnEO, is collected and disposed of for incineration and the relevant waste water streams are collected for incineration as far as technically and practically possible (noting planned improvements being implemented), RAC is of the opinion, that the operational conditions (OCs) and risk management measures (RMMs) in the exposure scenario are appropriate and effective in limiting the risk. Nevertheless, RAC recommends the applicant to further assess in any review report the feasibility to collect the remaining liquid wastes for adequate treatment and act on the outcome of the feasibility study.

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: 2.5 kg/year (2021) to 5 kg/year (2035) based on a release factor of 0.5 % (mass balance)
- Air: 0 kg/year
- Soil: 0 kg/year

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

Conclusions of RAC

RAC considers that the estimates for releases to the water provided by the applicant are appropriate. RAC did not identify shortcomings in the methodology used that would invalidate this conclusion. RAC notes, however, that the applicant did not support release estimates with measured release or emission data (instead using a batch-wise mass balance approach) and therefore recommends the applicant to perform a mass balance analysis after all new RMMs are implemented and to monitor releases of 4-tert-OPnEO and its principal degradation products in the waste water after on-site treatment and prior to release to the off-site waste water treatment plant (WWTP).

Does RAC propose additional conditions[3] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC propose monitoring arrangements[4] 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 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[5]

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

0.5-1 tonne/year

[3] 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.

[4] 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.

[5] 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*".

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

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

Kedrion S.p.A (hereafter referred to as "Kedrion") applied for the use of 4-tert-OPnEO as Triton X-100 (CAS 9002-93-1) to be used as a detergent for virus inactivation in the manufacturing of human plasma-derived medicinal products. There is a risk that viruses from the plasma donors could spread to the recipient of the medicinal product if nothing was done to remove the viruses from the raw material. The purpose of this use is to inactivate lipid-enveloped viruses potentially present in the raw material during the manufacturing process. The substance is used at Kedrion's facility in Sant' Antimo, Italy on approximately 100 days per year.

Usage of 4-tert-OPnEO in the facility was 438 kg in 2018 and the applicant envisions 5 % volume growth per year. This means that 4-tert-OPnEO usage is estimated at 483 kg in 2020 (i.e. the year in which new RMMs will be in operation) and 507 kg in 2021 (i.e. the first year after the sunset date). The maximum usage of 4-tert-OPnEO in the facility is envisaged to be 999 kg by 2035 and the total usage over the whole assessment period, i.e. 2021-2035, is estimated at 10 933 kg.

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

4-tert-OPnEO is used in the manufacturing process of three human plasma-derived medicinal products (Plasmagrade/Plasmasafe, Resusix and Plasminogen) to inactivate lipid-enveloped viruses potentially present in the raw material. Virus inactivation in plasma takes place during solvent/detergent (S/D) treatment, in which 4-tert-OPnEO and an organic solvent are mixed with the raw material and incubated for several hours in temperatures of 27-29 °C or 29-31 °C, depending on the product being treated. The 4-tert-OPnEO concentration is 1 % (w/w) of the total volume of plasma being treated. 4-tert-OPnEO is removed from the finished product via chromatography once the viral inactivation step is completed. The final plasma product contains less than 5 ppm 4-tert-OPnEO.

Table 1: Contributing Scenarios presented in the Use

Contributing scenario	ERC	Name of the contributing scenario	Size of the exposed population
ECS 1	ERC 4	Use at Sant' Antimo site	Not relevant

Storage within operations:

4-tert-OPnEO is delivered by truck in shipping cartons. These are placed on a pallet equipped with an accidental spill containment basin. In case of spill, all the material (liquid and solid) is collected in plastic tanks and sent to incineration as hazardous waste. The maximum amount stored at one time is 60 kg of 4-tert-OPnEO.

Solvent/detergent (S/D) treatment (same for Plasminogen process and for Plasmagrade/Plasmasafe and Resusix processes):

The amount of 4-tert-OPnEO needed is weighed under an aspiration hood according to the actual weight of the plasma pool. It is mixed together with other ingredients, such as an organic solvent, tri(n-butyl)phosphate (TNBP), and stirred to make a homogeneous mixture. The mixture is then added to the plasma pool. The washing water of the weighing and mixing

containers is sent to the waste water system.

Removal of S/D reagents (Plasmagrade/Plasmasafe and Resusix processes):

Castor oil is added to the mixture and extraction takes place under constant stirring. During this time, the mixture is cooled. Subsequently the plasma-oil emulsion is left to stand for some time in order to allow phase separation to occur. The organic layer contains the less polar of the two inactivants while 4-tert-OPnEO stays mostly in the aqueous phase. The aqueous phase is cleared by filtration after phase separation. The filtered plasma then passes through a cartridge which has been filled with a resin which holds back the 4-tert-OPnEO and at the same time lets plasma pass without significant retention of plasma components. When all the plasma has passed through the cartridge the resin is washed with ethanol solutions having increasing concentrations (from 25 % to 100 %).

Removal of S/D reagents (Plasminogen process):

No castor oil is added to the mixture and TNBP is mostly removed in the oily layer that forms when the mixture is allowed to stand. Due to limited capacity of the chromatographic columns used, only half of the aqueous phase (containing plasma and 4-tert-OPnEO) is sent to chromatography. The remaining portion (~50 %) is collected into suitable containers, classified as biological waste with the Code CER 180103* and sent to incineration. This portion contains half of the amount of 4-tert-OPnEO used. In this case the chromatographic columns bind only plasminogen molecules so that 4-tert-OPnEO is not held back by chromatographic column as well as the remaining components of plasma. This flow-through portion containing 4-tert-OPnEO is collected in plastic tanks and sent for incineration as biological waste (CER 180103*).

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

4-tert-OPnEO is used by the applicant to inactivate lipid-enveloped viruses. The polar head group of 4-tert-OPnEO disrupts the hydrogen bonds between lipid molecules in the lipid bilayer of the virus causing the lipid bilayer to decay. When the lipid bilayer decays, the viral genome is exposed and it can be destroyed by enzymes (nucleases) that are naturally present in blood (and in plasma). In addition, 4-tert-OPnEO helps to stabilise the organic solvent (TNBP), used in the S/D treatment.

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

4-tert-OPnEO is used in the manufacturing process of three human plasma-derived medicinal products*: Plasmagrade/Plasmasafe, Resusix and Plasminogen*. Out of these products, only Plasmagrade/Plasmasafe is currently available on the market whereas Resusix and Plasminogen are still in the clinical study phase and pre-registration, respectively. In its assessment, the applicant assumes that Resusix and Plasminogen will have been successfully brought to market by 2021.

Plasmagrade and Plasmasafe are two brand names for the applicant's S/D treated human plasma. Plasmagrade/Plasmasafe is a medicinal product used in different medical fields and by different healthcare professionals including transfusionists, transplantologists, emergency doctors, surgeons, haematologists, intensive care doctors, etc. The major therapeutic areas include transfusion medicine, liver/kidney transplantation, emergence rooms, intensive care and surgery.

Resusix is an S/D treated spray-dried plasma. It is being developed to provide a reliable

source of coagulation factors and volume replacement immediately, wherever needed, especially in emergency situations where storing conditions are of great importance. The major therapeutic areas include transfusion medicine, liver/kidney transplantation, emergency room, intensive care, surgery and haematology.

Plasminogen is the pre-commercialisation name of a therapy which has received orphan drug designation for the treatment of patients affected by congenital plasminogen deficiency and, in particular, ligneous conjunctivitis of the eye. Ligneous conjunctivitis is a rare form of chronic inflammation of the conjunctiva characterised by the formation of pseudo membranes on the palpebral surfaces of the eyes and progress to thick, white or yellow-white masses that replace the normal mucosa, which can lead to blindness. The pharmaceutical form as Plasminogen is eye drops for topical ocular use. Even though Plasminogen is not yet available on the market, approximately 25 patients worldwide have already been receiving treatment with this drug under expanded access programmes.

1. Operational Conditions and Risk Management Measures

1.1. Environment

The applicant presented one exposure scenario as described above with one environmental contributing scenario (ECS 1: Use at Sant' Antimo site) that includes storage within operations, S/D treatment, removal of S/D reagents (Plasminogen process; Plasmagrade/Plasmasafe and Resusix processes) and handling of waste – ERC 4 (Use of non-reactive processing aid at an industrial site).

No worker contributing scenarios are presented, as the scope of the CSR is limited to the environmental risk of 4-tert-OPnEO.

No contributing scenario for the service life of the final products is provided because the final product should not contain more than 5 ppm 4-tert-OPnEO.

Operational Conditions and Risk Management Measures in place for control of emissions to:

The Sant' Antimo site is compliant with EU "good manufacturing practice" (GMP) requirements as it produces medicinal products.

Waste

- Disposable items (bags, bottles, filters, pipes, accessories, gloves, overalls used in the process) that due to the possible contamination with biological material are classified as biological waste (CER 180103*) are collected for incineration by a certified contractor.
- Alcohol containing water (only for Plasmagrade/Plasmasafe and Resusix) is collected in specific tanks and sent as waste for incineration.
- Castor oil is collected and sent for incineration.
- The aqueous phase and the waste from the chromatographic columns are collected and sent for incineration.
- In case of spillage, all the materials are collected and sent for incineration as hazardous waste.

- In case of emergency maintenance, the content of the vessels is collected and disposed of as hazardous waste.
- Waste water coming from the washing of equipment (mixing containers, transfer silicone tubing, process tanks and etc.) is not collected for treatment and therefore identified as potential releases of 4-tert-OPnEO even after physico-chemical treatment in the on-site waste water treatment plant (WWTP) and subsequent release to the municipal WWTP.
- Sludge generated in on-site WWTP is collected and sent for incineration.
- Carbon filters from ventilation systems are replaced annually and sent for incineration.
- *By the end of the 2019, Kedrion is changing the procedure for the washing of flasks and beakers: disposable cleaning cloths will be used before washing the equipment and will be collected as waste after use and sent to incineration. In doing so, the applicant is planning to increase the quantity of 4-tert-OPnEO included in the waste sent for incineration from 98.3 % to 99.4 %. In response to RAC questions, the applicant confirmed its commitment to implement the new procedure by the end of 2019.*
- *By the end of the 2020, the switch from reusable to disposable tubing is planned to be implemented. In doing so, the applicant is planning to further reduce emissions from 0.57 % to 0.5 %. Thus the quantity of 4-tert-OPnEO included in the waste sent for incineration will increase further from 99.4 % to 99.5 %.*

Table 2: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	Semi closed systems	Considering the absence of elevated temperatures during the process and low vapour pressure of 4-tert-OPnEO, emissions to air are considered negligible.
Water	Incineration of solid and liquid waste	No residual releases assumed from waste water that is collected for incineration. Residual release originates from waste water that comes to on-site WWTP from the washing of equipment.
Soil	Very well controlled clean environment in the facility	Direct releases to soil are not possible. As the waste water leaving the Sant' Antimo site is discharged into a sewer and going to a municipal WWTP, residual release to the soil via application of sludge to agricultural soil cannot be excluded.

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

- All the internal areas, both warehouse and production areas have impermeable floors.
- Within the production of medicinal products, 4-tert-OPnEO is used either in closed systems or under chemical hoods which are equipped with activated carbon filters.
- The applicant follows the international standards for the EHS management system such as the OHSAS 18001, the ISO 14001 and has established an environmental management system according to EU Eco-Management and Audit Scheme (EMAS) regulation and is listed in the EMAS register.

- The site is under the IPPC Directive and is authorised by the local competent body (Campania's Region) with the AIA (integrated environmental authorisation).
- According to the EMAS, the site provides an annual Environmental Declaration that makes available its environmental data and, according the AIA, reports to the Region its monitoring plan.
- 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

Since all solid waste, which had been in contact with 4-tert-OPnEO, is collected and disposed of for incineration and the relevant waste water streams are collected for incineration as far as technically and practically possible (noting planned improvements being implemented), RAC is of the opinion, that OCs and RMMs in the exposure scenario are appropriate and effective in limiting the risk.

RAC notes that the applicant, in order to reduce emissions of 4-tert-OPnEO to the environment, is modifying the cleaning procedure of weighing containers. From the end of 2019 onwards, some of the containers (the flasks and beakers that could be contaminated with 4-tert-OPnEO) before washing will be cleaned with disposable cleaning cloths. These cloths will remove most of the 4-tert-OPnEO and will be sent for incineration. The information on mass balance analysis of the new procedure (based on an experimental study) was provided to RAC as confidential information.

RAC points out that some releases do occur due to the rinsing water of several devices used during the production process that are discharged to the on-site WWTP and after physico-chemical treatment further discharged to the municipal WWTP.

In their answers to RAC questions, the applicant explained that collecting rinsing waters and waste water of chromatography sequence steps separately on-site is not feasible as in order to do so, all the applicant's fixed installation would need to be completely restructured and it would represent a major change in terms of GMP. The applicant noted that it is technically difficult to separate rinsing water potentially contaminated with 4-tert-OPnEO from the rest of waste water generated in the facility (160 m^3/day). The applicant pointed out that it would be difficult and impractical to collect, store on-site and treat as hazardous waste all waste water produced in the facility before transporting it off site for incineration.

RAC notes that the applicant has assessed the technical viability of the additional risk management measures and/or operational conditions needed to ensure a complete collection of the effluents, i.e. prevention of emissions to water and acknowledges that the information provided indicates that the implementation of such measures has technical and organisational restraints. Nevertheless, RAC recommends the applicant to further assess the feasibility to collect the remaining liquid wastes for adequate treatment (see section 9).

1.3. Conclusions on OCs and RMMs

Overall conclusion

OCs and RMMs in the exposure scenario are appropriate and effective in limiting the risk.

Are the operational conditions and risk management measures appropriate[6] and effective[7] 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

Minor concerns with regard to the full effectiveness of the OCs and RMMs in place lead RAC to make recommendations for the review report, as 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-tert-OPnEO 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

Solid waste and waste water, with the exception of the release to water due to the rinsing water of several devices used during the production process, is collected for incineration. Therefore the environmental exposure assessment presented by the applicant is based on the residual release from rinsing reusable equipment for Plasmagrade/Plasmasafe and Resusix processes and from Plasminogen process.

The release per batch due to washing of equipment has been estimated as follows by the applicant:

- *Plasmagrade/Plasmasafe and Resusix processes*
  - (a) The residual liquid waste in the weighing container has been weighed and quantified to be 50 g 4-tert-OPnEO. The residual liquid waste in the mixing container and transfer silicone tubing has been weighed and quantified to be 16 g 4-tert-OPnEO. After introduction of a new cleaning procedure in the end of 2019 the emissions from step (a) will be reduced.
  - (b) The residual 4-tert-OPnEO in process tanks is diluted in washing water. The volume and concentration of the wash water has been quantified and used to calculate the residual 4-tert-OPnEO. The residual 4-tert-OPnEO was found to be 2.4 g.
  - (c) In the bulk solution the residual concentration of 4-tert-OPnEO is always below 5 ppm which is the acceptance limit for the plasma batch. If not, the product is rejected. Thus, considering a maximum amount of 10 kg plasma residue a maximum

[6] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[7] '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.

of 0.05 g of 4-tert-OPnEO could be going to the waste water via this last washing.

- (d) The column inlet silicone tube is multiuse and it is washed after each use; the washing water is sent to on-site WWTP. Assuming that the solution remaining on the inner surface is less than 10 % of the total inner volume, the residue 4-tert-OPnEO in the tube has been estimated by multiplying the concentration of 4-tert-OPnEO (in the solution passing through) by the 10 % of the tube inner volume. This calculation leads to 4 g.

Due to the changes in cleaning procedures during the step (a) 25 g of 4-tert-OPnEO will be going to waste water per batch of plasma in 2020.

- *Plasminogen process*
  - (a) The residual liquid waste in the weighing container has been weighed and quantified to be 50 g 4-tert-OPnEO. The residual liquid waste in the mixing container and transfer silicone tubing has been weighed and quantified to be 16 g 4-tert-OPnEO. After introduction of a new cleaning procedure in the end of 2019 the emissions from step (a) will be reduced.
  - (b) The residual 4-tert-OPnEO in process tanks is diluted in washing water. The volume and concentration of the wash water has been quantified and used to calculate the residual 4-tert-OPnEO. The residual 4-tert-OPnEO was found to be 2.4 g.
  - (c) In the finished product the residual concentration of 4-tert-OPnEO must be below 5 ppm which is the acceptance limit for the product. If not, the product is rejected. However the actual concentration has been measured and found below 0.3 ppm which is the quantification limit of the analytical method. Thus, considering a maximum amount of 10 kg plasma residue a maximum of 0.05 g of 4-tert-OPnEO could be going to the waste water via this last washing.

Due to the changes in cleaning procedures during the step (a) 21 g of 4-tert-OPnEO will be going to waste water per batch of plasma in 2020.

In the answers to RAC questions, the applicant pointed out that different processes cannot run at the same time and on the same batch of plasma. Thus, it was considered by the applicant that the max. 25 g of 4-tert-OPnEO will be released per batch during washing of the equipment.

In the answers to RAC questions, the applicant also noted that in order to further reduce emissions the switch from reusable to disposable tubing was also considered and is planned to be implemented by the end of 2020. In doing so, the applicant is planning to further reduce emissions from 0.57 % to 0.5 %.

Air

The applicant stated that due to the low vapour pressure of 4-tert-OPnEO, the low concentration in the formulation (< 1 %), the absence of elevated temperatures and the almost completely closed systems the emissions to air are negligible.

Soil

4-tert-OPnEO is handled indoor in a very well controlled clean room environment thus direct releases to soil are not possible. In its answers to RAC questions the applicant pointed out that all sludge generated in an on-site WWTP is collected and sent for incineration thus releases to the environment are avoided.

Table 3: Summary of environmental emissions of 4-tert-OPnEO

Release route	Release factor	Release per year in 2020	Release per year in 2021	Release per year in 2035	Release estimation method and details
Water	0.57 % in 2020 0.5 % in 2021 and after	2.75 kg	2.5 kg	5 kg	Release fraction to the municipal WWTP was calculated on the basis of the mass balance.

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-tert-OPnEO in mainly closed systems and collection for incineration of solid and key liquid wastes. RAC considers that the methodology for assessing the exposure from residual releases due to the rinsing water of several devices used during the production process to waste water is appropriate and the estimates provided by the applicant can be considered to be representative and are not likely to underestimate exposure. RAC notes, however, that the applicant did not support release estimates with measured release or emission data (instead using a batch-wise mass balance approach). Therefore, to get a better insight into the releases to the water compartment and to corroborate the effectiveness of the OCs and RMMs in place, RAC recommends the applicant to perform a new mass balance analysis and to implement a monitoring programme (see section 9).

As a result of the relatively low vapour pressure of 4-tert-OPnEO, the type of production processes and the RMMs and OCs in place, RAC concludes that releases to air are expected to be negligible.

Similarly, RAC agrees that direct releases to soil are not likely from the plant.

2.3. Conclusions on exposure assessment

RAC considers that the estimates for releases to the water 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-tert-OPnEO 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.

Based on the OCs and RMMs in the exposure scenario, the total amount of 4-tert-OPnEO used per year, the partly closed system production process and incineration of solid and liquid wastes, RAC is of the view that the applicant has 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).

The use applied for may result in emissions of the substance to the environment of up to 2.5 kg per year in 2021 with a maximum expected release of 5 kg per year in 2035.

3.2. Shortcomings or uncertainties in the risk characterisation

No shortcomings were identified in the risk characterisation.

3.3. Conclusions on risk characterisation

RAC is of the view that the applicant has 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[8]

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

0.5-1 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

According to the applicant, a proposed alternative should meet the following requirements:

- Same or better virus reduction factor as TNBP and 4-tert-OPnEO (at least 4 log reduction in virus quantities);
- Same product quality in terms of protein content and activity;
- The solvent/detergent is effectively removed from the product to residual values;
- The product is not toxic.

The applicant has performed a literature review to identify alternative detergents used for virus inactivation in the production of S/D treated human plasma. The applicant identified three potential alternative detergents: Tween 80 (polyoxyethylene (80) sorbitan monooleate), sodium cholate and lauryldimethylamine N-oxide (LDAO).

Sodium cholate and LDAO have not been considered for further investigation by the applicant. For sodium cholate the applicant explained that its use in plasma manufacturing processes is effectively prohibited because of its bovine origin. For LDAO the applicant identified one study using the substance for virus inactivation. However, as in the identified study LDAO was used for the manufacture of monoclonal antibodies and Fc-fusion proteins rather than for the manufacture of plasma-derived products, the applicant did not consider

[8] 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*".

the substance further.

Only Tween 80 has been further investigated by the applicant because it has been used for viral inactivation in plasma-derived products in the past and because it can be removed from the product by a single chromatography step. The applicant intends to conduct further feasibility testing of Tween 80 in its processes.

The applicant stated that it is, at the same time, in contact with its chemical suppliers about new potential alternatives. Responding to questions by SEAC, the applicant clarified that two new potential alternative detergents, TDAO (N,N-dimethyltetradecylamine N-oxide) and Nereid, have been identified from this stream of work. TDAO and Nereid are still under development by the chemical suppliers and the applicant clarified in response to a SEAC question that feasibility testing of these two new alternatives will not start before the beginning of 2020.

Apart from alternative detergents, the applicant also provided information on alternative viral inhibition technologies that would make the use of S/D treatment obsolete. The discussed alternative technologies include precipitation with ethanol, pasteurisation or heating in aqueous solution, low pH treatment and nanofiltration. For each of the concerned products – Plasmagrade/Plasmasafe, Resusix and Plasminogen – the applicant detailed why these alternative technologies are not feasible. Generally speaking, the alternative technologies are meant to be used in the production of specific coagulation factors, specific plasma proteins (e.g. albumin) and immunoglobulins, but the applicant's products are made of whole plasma, where all the proteins and coagulation factors and other active components have to be retained in an active state. As a result the applicant stated that substitution efforts are focused on alternative detergents, which would also mean that there is no need for a major change in the production process (e.g. new design of the manufacturing equipment).

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 detergents. The identification of potential alternative detergents is based on a literature review and the applicant's contacts with its chemical suppliers. SEAC further notes that the applicant clearly set out the functional requirements a proposed alternative would have to meet. Even though initially the application did not systematically address aspects of technical and economic feasibility as well as availability of the short-listed alternatives, such information, including for two newly identified potential alternatives, has been provided in response to a SEAC request. 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

The applicant has investigated the viral inactivation effectiveness of Tween 80 by using it together with TNBP as a solvent for S/D treatment of human plasma spiked with model viruses in a down-scaled version of the manufacturing process. The results indicate that TNBP/Tween 80 is capable of effectively inactivating the investigated viruses.

However, the applicant stated that for the Plasmagrade/Plasmasafe and Resusix manufacturing processes it is also necessary to demonstrate the effectiveness of TNBP/Tween 80 to inactivate more resistant viruses, such as the Vaccinia virus. This is because S/D treatment is the only viral inactivation step in the Plasmagrade/Plasmasafe and Resusix manufacturing processes. According to the applicant, data taken from the scientific literature indicate that there are deficiencies in the viral inactivation capabilities of TNBP/Tween 80 when compared to TNBP/4-tert-OPnEO. In response to SEAC questioning, the applicant explained that it nevertheless intends to carry out further tests to assess the feasibility of Tween 80 in their processes in practice. According to the timelines provided, viral safety investigation studies will take place in 2020 for Plasmagrade/Plasmasafe and Resusix and in 2019 for Plasminogen.

For Plasminogen, virus inactivation is performed in two different steps, S/D treatment and nanofiltration, and according to the applicant there is no need to demonstrate the effectiveness of S/D treatment with regards to the Vaccinia virus. The applicant, therefore, plans to proceed with a feasibility study at bench scale, planned to start in 2019, to demonstrate the ability of the currently used affinity chromatography step to remove Tween 80 from the Plasminogen product. According to the timelines provided, bench scale experiments are planned to conclude in the first quarter of 2021.

With regard to the two newly identified potential alternatives, TDAO and Nereid, the applicant stated that both are still under development by its chemical suppliers. The applicant is planning feasibility testing of TDAO and Nereid in the manufacture of Plasmagrade/Plasmasafe, Resusix and Plasminogen. In response to a SEAC question the applicant clarified that these tests will, however, not start before the beginning of 2020 as neither of the two alternatives will be available to the applicant before that.

SEAC requested the applicant to provide a short summary of the current status with regard to technical and economic feasibility as well as availability of the short-listed alternatives as these elements were not described systematically in the application. The applicant provided the requested information for Tween 80, TDAO and Nereid. Tween 80 is currently not deemed technically feasible as both its capability to inactivate more resistant viruses (e.g. Vaccinia) and its capability to be removed from the end product still have to be assessed. Regarding economic feasibility, the applicant explained that the change in raw material costs associated with a switch to Tween 80 would be insignificant. Tween 80 is also considered to be readily available in the required purities through multiple vendors. The technically feasibility of both TDAO and Nereid is currently unknown as feasibility testing is yet to be

started. As both substances are still under development, the outlook in terms of economic feasibility and availability is not yet fully clear.

Even though the applicant has not yet identified an alternative detergent to eventually replace 4-tert-OPnEO, an estimate of substitution costs has been provided. Based on past R&D experience, the applicant estimated total substitution costs of €83 million (not discounted) for Plasmagrade/Plasmasafe, Resusix and Plasminogen. According to the applicant, a substantial part of these costs stems from the non-clinical and clinical studies that are required to demonstrate that the products manufactured with alternative detergent are safe for patients.

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 due to the need to ensure the performance of any potential alternatives and the required non-clinical and clinical studies as well as regulatory approval processes.

Tween 80 is currently being considered for further feasibility testing by the applicant. In parallel, the applicant is planning to start feasibility testing of two newly identified potential alternatives, TDAO and Nereid, once these are made available by its chemical suppliers. SEAC notes that even if an alternative appears to be technically feasible during initial research, its successful implementation, including the studies needed to demonstrate products are safe for patients, would extend far beyond the sunset date.

With regard to substitution costs, SEAC agrees with the applicant's conclusion that these are likely to constitute a substantial investment given the required non-clinical and clinical studies and regulatory approval processes.

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

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 which refers to the applicant's GMP (Good Manufacturing Practice) certification which requires it to keep detailed documentation at all stages of product development. The applicant further stated that the substitution of 4-tert-OPnEO will be done in accordance with standardised operating instructions whose implementation will be monitored by the applicant's project management office.

The applicant is engaged in substitution activities and R&D but has so far not been able to identify a suitable alternative to replace 4-tert-OPnEO in its manufacturing processes. The

applicant is performing further feasibility testing for the use of Tween 80 in its processes and is planning to start feasibility testing of two newly identified potential alternatives, TDAO and Nereid, once these are made available by its chemical suppliers. The applicant estimated that testing of TDAO and Nereid would start in the beginning of 2020.

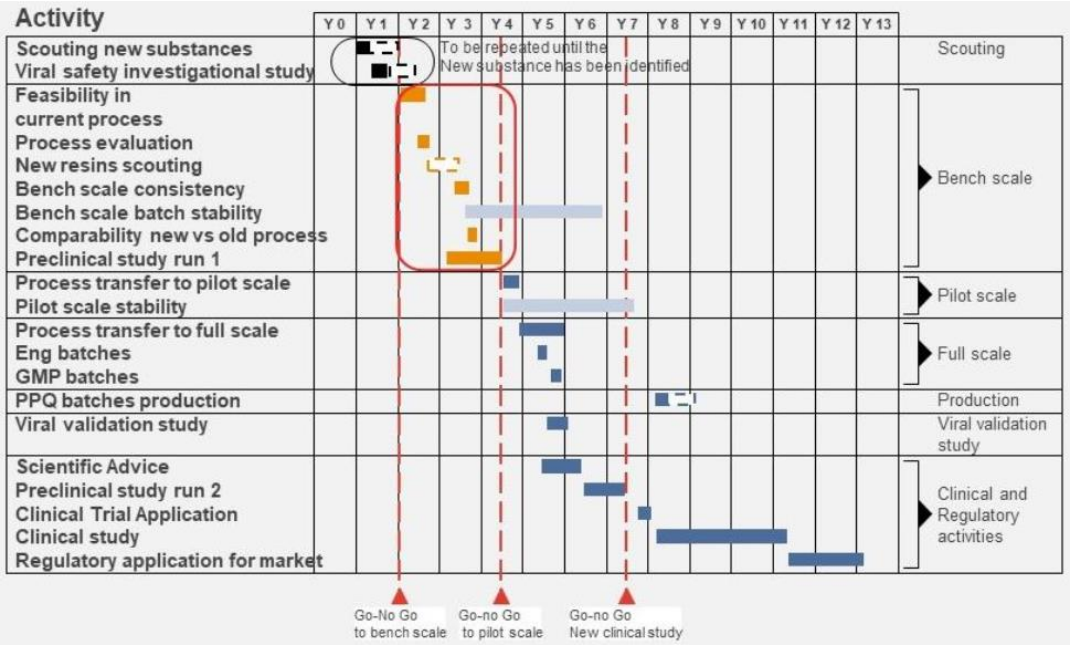
Irrespective of the alternative detergent eventually chosen for substituting 4-tert-OPnEO, a series of steps needs to be completed for all three concerned products following the identification of a potential alternative. The applicant described the main steps to be completed, including validation tests and process transfer from bench scale through pilot scale to full scale. In addition, the applicant stated that it would need to show that the products manufactured using an alternative are safe for patients, which requires non-clinical toxicological studies and clinical studies, and it would need to get regulatory approval from the relevant medicinal products authorities.

For each of the three concerned products, the applicant provided a timeline showing the estimated duration of the activities that have to be carried out under each of the main steps. SEAC notes that the substitution timelines are to a large extent driven by the required non-clinical and clinical studies. For each of the three products, non-clinical and clinical studies account for approximately two and four years, respectively, of the estimated time needed for substitution. The applicant substantiated the long duration of these steps by detailing the battery of non-clinical toxicological studies and the required steps for the necessary clinical studies.

According to the timelines provided, the applicant estimated that the time needed after the sunset date to achieve full substitution would be 11 years for Plasmagrade/Plasmasafe (see **Figure 1**), 16 years for Resusix (see **Figure 2**) and 12 years for Plasminogen (see **Figure 3**). The applicant explained that differences in the substitution timelines of the three products reflect different requirements in terms of non-clinical and clinical studies.

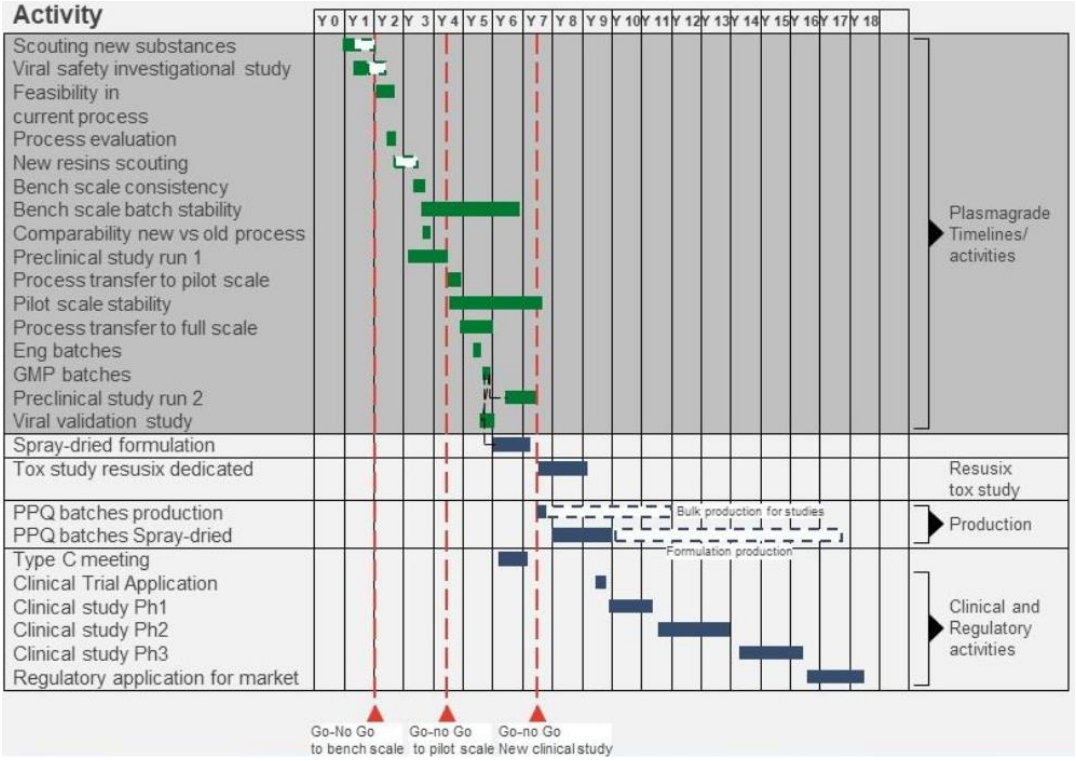
The applicant stated that the substitution timeline, and by extension the requested review period, is based on the steps that follow the selection of an alternative detergent. Based on the projected substitution timeline the applicant requested a review period of 15 years. SEAC notes that, according to the applicant's estimated timelines, substitution of 4-tert-OPnEO in Plasmagrade/Plasmasafe and Plasminogen could be attained within a long review period (12 years), while the requested review period (15 years) would not be sufficient for Resusix (16 years according to **Figure 2**). In response to a question by SEAC the applicant explained that Resusix has a shelf life of two years and that enough batches of Resusix could be produced during the 15th year of the requested review period to cover demand until the remaining substitution work is completed. The applicant further explained that the production of Resusix would then cease at the end of the requested review period until Resusix produced with an alternative has received market authorisation.

Figure 1: Substitution timeline for Plasmagrade/Plasmasafe



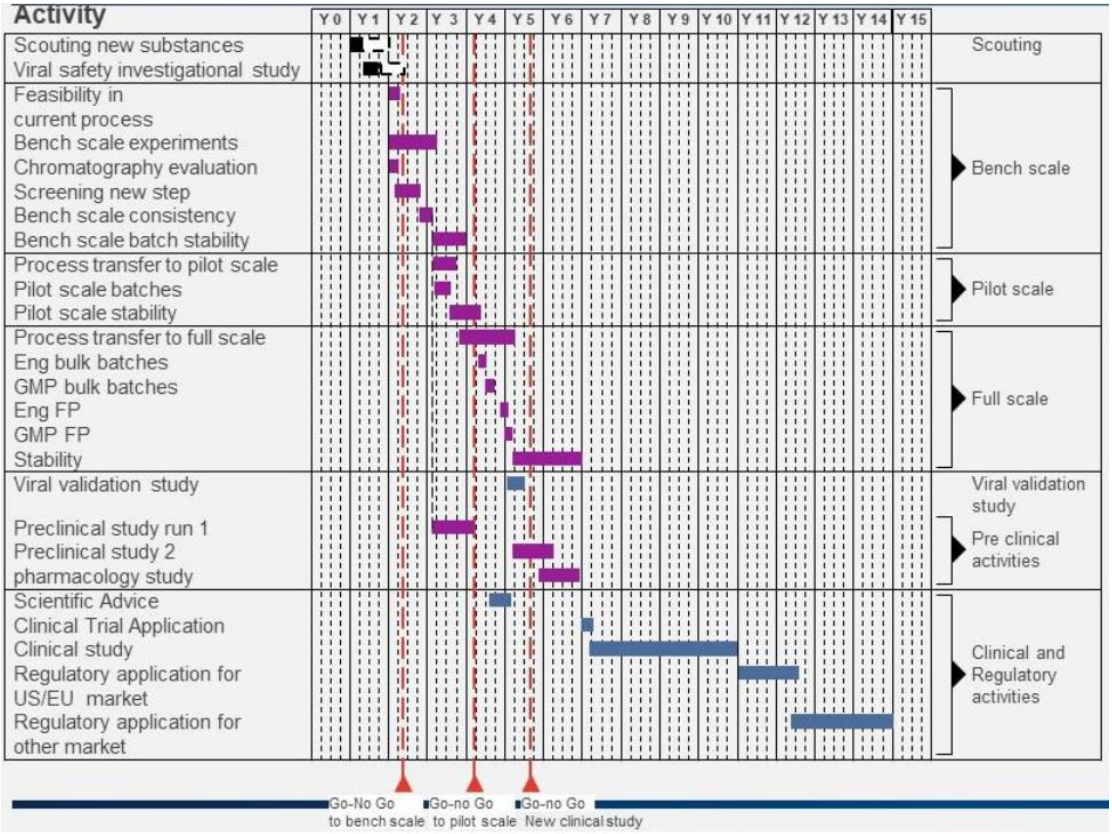
Note: It is assumed that year 1 in this case is 2020 and therefore substitution would be finished in 2032, which is 11 years after the sunset date.

Figure 2: Substitution timeline for Resusix



Note: It is assumed that year 1 in this case is 2020 and therefore the substitution would be finished in 2037, which is 16 years after the sunset date.

Figure 3: Substitution timeline for Plasminogen



Note: It is assumed that year 1 in this case is 2019 and therefore the substitution would be finished in the end of 2032, which is 12 years after the sunset date.

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. In particular given the duration of the required non-clinical and clinical studies, SEAC finds credible the applicant's conclusion that the substitution timeline would extend far beyond the sunset date. However, SEAC notes that for two of the three utilisations in the scope of the use applied for (Plasmagrade/Plasmasafe and Plasminogen), substitution could be completed in a shorter time than the 15-year review period requested by the applicant.

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, 4-tert-OPnEO contaminated waste – consisting of disposable items (bags, bottles, filters, pipes, accessories, gloves, overalls), alcoholic water (only for Plasmagrade/Plasmasafe), castor oil, and the aqueous phase and the waste from the chromatographic column – is collected and incinerated by a certified provider. Releases to the environment only occur from the washing of contaminated equipment. The applicant first treats its waste water on-site before discharging it into a sewer after which it is treated by the municipal waste water treatment plant. In response to a SEAC question, the applicant clarified that the releases will eventually occur in the Gulf of Naples, located in the Tyrrhenian Sea, which is part of the Mediterranean Sea.

The applicant estimated that currently 1.7 % of the total amount of 4-tert-OPnEO used is released to the environment. Applying a release factor of 1.7 % to the total projected use of 4-tert-OPnEO over the requested review period (10 933 kg), the applicant estimated that 186 kg of 4-tert-OPnEO could be released to the environment over the 2021-2035 period.

The applicant applied a release factor of 1.7 % even though it described plans to implement a change in the washing procedure for flasks and beakers before the sunset date (by the end of 2019). According to the applicant, this change would reduce the release factor from 1.7 % to 0.6 %. In response to a request by the Committees, the applicant explained that releases were estimated using the higher release factor as it represents the current situation. However, the applicant also confirmed that the lower release factor will be obtained when the improved cleaning procedures are in place at the end of 2019. Furthermore, in response to a question by RAC, the applicant noted that a switch from reusable to disposable tubing is planned to be implemented by the end of 2020 which will lead to a further reduction in the release factor from 0.6 % to 0.5 %. SEAC notes that using the release factor of 0.5 % would result in estimated releases of 4-tert-OPnEO of around 55 kg over the 2021-2035 period (calculated by applying the release factor of 0.5 % to the total projected use of 4-tert-OPnEO over the requested review period, i.e. 10 933 kg × 0.5 % = 55 kg).

In response to questioning by the Committees, the applicant explained that eliminating the remaining 4-tert-OPnEO releases to the environment would not be technically nor economically feasible as it would imply the collection, storage, transportation and incineration of 160 m^3 waste water per day. The applicant did not provide an economic assessment of the necessary extension of its collection and treatment system and of the cost to transport and incinerate the liquid waste. SEAC recognises however that incineration as waste water treatment is associated with costs as well as emissions of air pollutants and carbon dioxide and in some situations may require the use of fossil fuels.

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

5.2. Benefits of continued use

Non-use scenario

According to the applicant, the most likely non-use scenario is the cessation of production of Plasmagrade/Plasmasafe, Resusix and Plasminogen. The applicant clarified in response to a SEAC request that, since Resusix and Plasminogen are not yet on the market, the non-use scenario for these two products would be to stop their development. The applicant also explained in its response that a permanent production shutdown is justified on the basis of the complex and lengthy regulatory process needed to ensure GMP compliant manufacturing of human plasma-derived medicinal products and the complex technology in use.

SEAC also asked the applicant whether a temporary production shutdown until substitution is completed was considered. The applicant responded that this is not an option as its market position for Plasmagrade/Plasmasafe would be lost during the time needed to substitute. The applicant stated that it would also abandon the development of the other products if these could only be commercialised after successful substitution.

SEAC agrees that given the specificity of the concerned product and markets, cessation of production of Plasmagrade/Plasmasafe and stopping the development of Resusix and Plasminogen is a credible non-use scenario for the applicant.

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?

- 69 jobs would be lost

Socio-economic impacts of continued use

The applicant stated the main impacts of the non-use scenario as follows:

- Economic impacts on Kedrion's activities, including loss of revenues and costs related to substitution;
- Impacts on hospitals and patients related to unavailability of Plasmagrade/Plasmasafe, Resusix and Plasminogen;
- Social impacts related to job losses;
- Other social or wider economic impacts on the Italian healthcare system and related to reputational damage.

Economic impacts

The applicant provided monetised economic impacts in terms of lost revenues and costs related to substitution. The applicant estimated that the revenues associated with the three products which depend on 4-tert-OPnEO – Plasmagrade/Plasmasafe, Resusix and Plasminogen – amount to €1 026 million (in present value terms, discounted at 4 %) over the 15-year review period applied for. SEAC notes, however, that revenue is not a good indicator of benefits to society and that the focus should instead be on profit because this recognises that both revenues and costs can vary in response to changes in output. The applicant did not provide profit forecasts as such but instead stated that profits represented 29 % of revenues in 2017. Assuming a constant profit rate of 29 % over the requested review period and using the provided revenue estimates as a basis, the applicant derived a profit loss estimate of €298 million for the period 2021 to 2035 (the requested review period).

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 €20 million (calculated as €298 million divided by the length of the assessment period, i.e. 15 years). This value is taken forward by SEAC for the cost-effectiveness analysis.

The applicant's analysis assumed that total revenue for the three concerned products will steadily grow over the requested review period. It is further assumed that Resusix and Plasminogen, products which are currently being developed, will have been successfully brought to market by 2021 and that both products are of high value once commercialised. SEAC asked the applicant for further substantiation of the optimistic assumptions underlying the revenue forecasts. The applicant explained that medical needs addressed by Resusix and Plasminogen are either unmet or will be increasing. Despite the arguments seeming valid, SEAC notes a lack of supporting evidence (market and competition analysis) and that the economic impacts incurred by the applicant in the non-use scenario could be significantly overestimated due to the optimistic assumptions underlying the revenue (and profit) forecasts.

The applicant also calculated costs of €55 million (in present value terms, discounted at 4 %) for the development of an alternative to 4-tert-OPnEO as economic impact. SEAC sought clarification as to the basis of this figure. In response, the applicant confirmed that substitution costs are incurred in the non-use scenario. However, SEAC considers that substitution costs are not incurred in the non-use scenario since the applicant declared that production will stop in case an authorisation for the use applied for is not granted. Therefore, substitution costs will not be considered by SEAC as an additional benefit of continued use and considers that substitution costs are reflected in the applicant's profit estimate.

Impacts on hospitals and patients

The applicant also considered that the unavailability of its products in the non-use scenario would have impacts on hospitals and patients. With regard to Plasmagrade/Plasmasafe, even though there are EU competitors producing S/D treated plasma, according to the applicant, these are all using 4-tert-OPnEO for virus inactivation as well and no plasma S/D products are authorised in the EU from non-EU manufacturers. As a result, at least in the short run, hospitals would have to switch to fresh frozen plasma which has not been S/D treated but for which plasma collection centres have to use their own in-house virus inactivation kits. The applicant stated that these in-house inactivation kits have inferior performance and have only limited availability. As regards Resusix, the applicant stated that it would be the only S/D treated plasma product using spray-dried technology available on the market but that its development would have to be abandoned in the non-use scenario. As Plasmagrade/Plasmasafe and Resusix are used in many therapeutic areas (see Section 0.3) the non-use scenario would have a negative impact on the treatment of patients.

With regard to Plasminogen, in the non-use scenario the currently developed drug would not become available on the market and, since no similar drug is currently available, hospitals would have to resort to suboptimal treatment options like membranes excision surgery according to the applicant. This would have negative impacts on the quality of life of patients who would have to undergo surgery instead of using Plasminogen eye drops. Moreover, insufficient treatment of ligneous conjunctivitis can lead to visual impairment and blindness. The applicant provided monetised health impacts related to avoided cases of visual

impairment and blindness based on the estimated prevalence of ligneous conjunctivitis in the EU and mean annual expenses per patient for visual impairment and blindness taken from a review study[9]. According to the applicant, the costs of additional visual impairment and blindness cases for the requested review period would be between €37 million and €72 million depending on the severity of visual impairment. Even though SEAC acknowledges the benefits to patients associated with Plasminogen treatment, SEAC also notes a number of shortcomings in the estimated monetised health impacts as the applicant's analysis assumes that: Plasminogen will have been brought successfully to market by 2021; all patients suffering from ligneous conjunctivitis would receive the drug and treatment is successful; in the non-use scenario no patient would receive alternative treatment in the form of surgery; and no similar drugs would be marketed by competitors throughout the requested review period. Moreover, the applicant only considered direct medical costs associated with visual impairment and blindness but not indirect costs related to productivity losses, pre-mature mortality or morbidity. The net effect of these shortcomings is difficult to assess. SEAC therefore cannot rely on the monetised estimate provided by the applicant for the cost-effectiveness analysis.

Social impacts related to job losses

The applicant also estimated that in case of a non-granted authorisation the equivalent of 69 directly associated jobs would be lost – accounting for about 40 % of Kedrion's workforce at the Sant' Antimo site. To estimate the associated social cost of unemployment the applicant used the default welfare cost factor for Italy outlined in Dubourg (2016)[10] and endorsed by SEAC (2016)[11]. This results in a value of €13.5 million. SEAC takes note of this calculation and that it is restricted to only estimating the direct potential costs of non-use on the applicant's own workforce.

Other social or wider economic impacts

Other social or wider economic impacts have not been quantified, although the applicant notes potentially strong impacts of non-use on the Italian healthcare system given the applicant's high market share of Plasmagrade/Plasmasafe in Italy. The applicant also states that it would suffer from reputational damage due to the loss of activities related to rare diseases and orphan drug development.

Distributional impacts

The applicant provided only very limited information on the expected distributional impacts. According to the applicant, in the non-use scenario only manufacturers of competitive products might gain while other stakeholders or socio-economic groups (including suppliers, hospitals and patients) would suffer. However, in the applicant's view any positive impacts on competitors would not be immediate due to a lack of capacity and skills to replace the products concerned by the use applied for. SEAC does not see the analysis of distributional impacts as critical for its views on the socio-economic analysis.

[9] Köberlein et al. (2013): The economic burden of visual impairment and blindness: a systematic review. BMJ Open 2013;3:e003471. doi: 10.1136/bmjopen-2013-003471

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

[11] SEAC (2016): https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25

Table 4: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts (over the 15-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[1]	Not relevant
1.2 Avoided profit loss due to ceasing the use applied for[2]	€20 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	*€20 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	€13.5 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.)[3]	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	*€13.5 million*
3. Aggregated socio-economic benefits (1+2)	**€33.5 million**

Notes:

1. SEAC did not consider the applicant's estimate of substitution costs as explained under *Economic impacts* in Section 5.2 above.
2. SEAC considered one year of profit loss only as explained under *Economic impacts* in Section 5.2 above.
3. SEAC did not consider the applicant's estimate of monetised health impacts related to avoided cases of visual impairment and blindness as explained under Impacts on hospitals and patients in Section 5.2 above.

5.3. Combined assessment of impacts

The applicant assessed that the monetised costs of the non-use scenario would consist of €298 million of profit losses, €55 million of substitution costs and €37 million of costs related to additional visual impairment and blindness cases and €13.5 million of social impacts related to job losses over the 15-year assessment period. The applicant considered only the first three of these elements, amounting to €390 million, in a cost-effectiveness analysis. The applicant did not consider the social impacts related to job losses and other qualitatively described impacts (i.e. impacts on patients and hospitals as well as other social or wider economic impacts) in the quantitative comparison of impacts. The applicant estimated that 186 kg of 4-tert-OPnEO releases to the environment could be avoided in the non-use scenario. This gives a cost-effectiveness ratio of €2.1 million per kg of 4-tert-OPnEO releases avoided. This is considered disproportionate by the applicant.

As noted in Section 5.2, SEAC only considers one year of lost profits, amounting to €20 million, for the cost-effectiveness analysis. Furthermore, including the applicant's estimate of substitution costs in the socio-economic analysis risks overstating the economic impact of the non-use scenario. Moreover, for the reasons outlined in Section 5.2, SEAC

cannot consider the applicant's estimate of monetised health impacts related to avoided cases of visual impairment and blindness. On the other hand, the applicant did not include the monetised social impacts related to job losses in the cost-effectiveness analysis. Furthermore, as outlined in Section 5.1, following the implementation of additional RMMs before the sunset date, releases of 4-tert-OPnEO are estimated at 55 kg over the 2021-2035 period. SEAC notes that considering only one year of lost profits, excluding substitution costs and the estimated monetised health impacts but including social impacts related to job losses in the quantitative comparison of impacts and considering released quantities of 55 kg would result in a cost-effectiveness ratio of €0.6 million per kg of 4-tert-OPnEO releases avoided.

SEAC notes, however, that this calculation is based on the applicant's optimistic assumption with regard to the development of revenue (and profit) for the not yet marketed products Resusix and Plasminogen. At the request of SEAC, the applicant provided information on profit losses related to the already marketed products only (Plasmagrade/Plasmasafe). In addition to SEAC's cost-effectiveness calculations described in the previous paragraph, SEAC also took a more conservative approach restricting lost profits to the already marketed product only. Even though the relevant quantitative information is claimed confidential by the applicant and is hence not presented in the opinion, SEAC notes that adopting such a conservative approach does not change the conclusions on the appropriateness of the applicant's assessment.

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

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€33.5 million (over the 15-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	Impacts on hospitals and patients related to unavailability of Plasmagrade/Plasmasafe, Resusix and Plasminogen Other social or wider economic impacts on the Italian healthcare system and related to reputational damage	Additional qualitatively assessed risks	Environmental impacts associated with releases of 4-tert-OPnEO of 55 kg (over the 15-year assessment period)
Summary of socio-economic benefits	**Aggregated socio-economic benefits: €33.5 million (over the 15-year assessment period)** **Impacts on hospitals and patients, other social or wider economic impacts**	**Summary of excess risk**	**Environmental impacts associated with releases of 4-tert-OPnEO of 55 kg (over the 15-year assessment period)**

Table 6: Cost of non-use per kg

	Over the 15-year assessment period
Total cost[1] (€)	€33.5 million
Total emissions[2] (kg of 4-tert-OPnEO)	55 kg
Ratio[3] (€/kg of 4-tert-OPnEO)	€0.6 million/kg of 4-tert-OPnEO

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 15-year assessment period, based on Table 3
3. "Ratio" = Total cost/Total emissions

5.4. SEAC's view on Socio-economic analysis

SEAC's detailed views on the non-use scenario and its credibility, economic impacts, impacts on hospitals and patients and social impacts related to job losses can be found in Section 5.2 above. Overall, SEAC agrees with the non-use scenario and with the applicant's quantitative assessment of economic impacts although some shortcomings have been identified following SEAC scrutiny. In particular, SEAC did not consider it relevant to include substitution costs as economic impacts given that the applicant's non-use scenario is a permanent production shutdown of the concerned products. Moreover, the economic impacts incurred by the applicant in the non-use scenario could be significantly overestimated due to the optimistic assumptions underlying the estimated profit losses related to the products not already on the market. SEAC also agrees with the calculations of social costs related to job losses and, even though the applicant's estimate of monetised impacts on patients' health are not sufficiently robust to be taken into account, has no major comments on the qualitative description of impacts on hospitals and patients.

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, keeping in mind that economic impacts as stated by the applicant could be overestimated.

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 has requested a review period of 15 years and justified it for each product by the time needed to carry out validation tests and process transfer from bench scale through pilot scale to full scale, non-clinical toxicological studies and clinical studies, as well as regulatory approval processes.

According to the substitution timelines presented by the applicant, the time needed after the sunset date to complete substitution is 11 years for Plasmagrade/Plasmasafe (currently on the market), 12 years for Plasminogen (to be put on the market in the future) and 16 years for Resusix (to be put on the market in the future). As described in Section 4.4 above, in the case of Resusix, the applicant clarified that an anticipated increase in production would make it possible to manage with a 15-year review period despite a duration of 16 years for the substitution process as described in the application.

Due to high performance requirements, the non-clinical and clinical studies required to demonstrate that the products manufactured using an alternative to 4-tert-OPnEO are safe for patients and the regulatory approval process, SEAC finds it credible that it would not be possible for the applicant to substitute within a normal review period.

However, the document CA/101/2017 of the European Commission setting criteria for review periods longer than 12 years stipulates that a review period longer than 12 years can only be granted if there are no suitable alternatives for any of the utilisations under the scope of the use applied for. In the present application, substitution is feasible in 11 years for Plasmagrade/Plasmasafe (the only marketed product), therefore the case does not qualify for a review period longer than 12 years.

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

7. Proposed additional conditions for the authorisation

Were additional conditions[12] proposed for the authorisation?

☐ Yes

☒ No

7.1. Description

RAC

Proposed additional conditions

Not relevant.

SEAC

Proposed additional conditions

Not relevant.

7.2. Justification

RAC is of view that:

- the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible based on the OCs and RMMs in the exposure scenario;
- the estimates for releases provided by the applicant are appropriate.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[13] proposed for the authorisation?

☐ Yes

☒ No

8.1. Description

Not relevant.

8.2. Justification

RAC is of view that:

- the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible based on the OCs and RMMs in the exposure scenario;

[12] 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.

[13] 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.

- the estimates based on a measured, batch-wise mass balance for releases to the environment provided by the applicant are appropriate.

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1 Description

RAC recommends the applicant to further assess in any review report the feasibility to collect the remaining liquid wastes for adequate treatment and act on the outcome of the feasibility study.

RAC recommends that the applicant should, after implementation of all new RMMs, perform a new mass balance analysis in order to confirm the predicted effectiveness of the implemented RMMs and report the results in any review report.

RAC recommends also that the applicant should monitor at least quarterly/four times per year (during the time of operation) 4-tert-OPnEO and its principal degradation products in the waste water after on-site treatment and prior to release to the off-site WWTP using an analytical method capable of adequately characterising the substance and its principal degradation products in water at an appropriately low level of quantification. The results should be included in any review report, including details of sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.

9.2. Justifications

RAC observes that relevant solid and liquid wastes are collected for treatment by incineration. Residual releases of 4-tert-OPnEO originate from waste water that comes to on-site WWTP from the washing of equipment. RAC recommends the applicant to further asses in a potential review report the feasibility to collect these remaining liquid wastes.

RAC notes that the applicant did not support release estimates with measured release or emission data (instead using a batch-wise mass balance approach). Therefore, RAC recommends the applicant to perform a mass balance analysis after implementing the new RMMs in order to confirm their predicted effectiveness. Furthermore, RAC is of the opinion that, in order to substantiate estimated releases to waste water, the applicant should monitor 4-tert-OPnEO and its principal degradation products in the waste water after on-site treatment and prior to release to the off-site WWTP. 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 OCs and RMMs in place and to confirm that emissions are reduced to as low a level as 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).

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