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, ethoxylate, covering well-defined substances and UVCB substances, polymers and homologues (Triton™ X-100, Triton™ X-405, Triton™ X-705):

Use #4: Use of IVD kit reagents on diagnostic analyser systems

Submitting applicant

Siemens Healthcare Diagnostics Products GmbH

ECHA/RAC/SEAC: AFA-O-0000006838-59-04/F

Consolidated version

Date: 17/09/2020

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	**Siemens Healthcare Diagnostics Products GmbH** (position in supply chain: downstream
Substance ID EC No CAS No	**4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated** 618-344-0 9002-93-1
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) - effects to the environment
Use title	**Use of IVD kit reagents on diagnostic analyser systems**
	Other connected uses: Use 1: Use of 4-tert-OPnEO in isolation protein from cell cultures Use 2: Use of 4-tert-OPnEO in formulation of IVD-kit reagents Use 3: Use of 4-tert-OPnEO in formulation IVD wash solutions Use 5: Use of IVD-wash solutions on diagnostic analyser systems
	Same uses applied for:
Use performed by	☐ Applicant ☒ Downstream Users of the applicant
Use ID (ECHA website)	0154-04

Reference number	11-2120816702-60-0004
RAC Rapporteur	Lina DUNAUSKIENĖ
SEAC Rapporteur SEAC Co-rapporteur	Andreas LÜDEKE Žiedūna VASILIŪNĖ
ECHA Secretariat	Christiaan LOGTMEIJER Pablo REGIL Daniele PENNESE

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	20/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	01/08/2019
Application has been submitted by the Latest Application Date for the substance and applicant and their DUs can benefit from the transitional arrangements described in Article 58(1)(c)(ii).	☒Yes ☐No
Public 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:
Request for additional information in accordance with Article 64(3)	On 17/09/2019 and 04/08/2020 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23821/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	Not held – no new information submitted in public consultation, no need for additional information/discussion on any technical or scientific issues related to the application from the rapporteurs
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant	☐Yes, by [date] Reason: e.g. due to the need to ensure the efficient use of resources, and in order to synchronise the public consultation with the plenary meetings of the Committees. ☒No
The application included all the necessary information specified in Article 62 that is relevant to the Committees' remit.	☒Yes ☐No Comment:

Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	RAC: 13/03/2020, agreed by consensus.
	SEAC: 12/03/2020, agreed by consensus.
Date of sending of the draft opinion to applicant	11/05/2020
Date of decision of the applicant to comment on the draft opinion, in accordance with Article 64(5)	11/06/2020
Date of receipt of comments in accordance with Article 64(5),	23/07/2020
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 17/09/2020, adopted by consensus.
	SEAC: 17/09/2020, adopted by consensus.
Minority positions	RAC: ☒N/A
	SEAC: ☒N/A

THE OPINION OF RAC

RAC has formulated its opinion on:

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

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

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

RAC concluded that the operational conditions and risk management measures described in the application are **not** appropriate and effective in limiting the risk to the environment.

The proposed additional conditions for the authorisation are expected to result in operational conditions and risk management measures that are appropriate and effective in limiting the risk to the environment.

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

The use applied for may result in emissions of 200-400 kg/year of the substance to the environment for a total of 1 000-10 000[1] downstream users' sites (i.e. an average per site up to 0.02-0.4 kg/year)

THE OPINION OF SEAC

SEAC has formulated its opinion on:

- the socio-economic factors, and
- the suitability and availability of alternatives associated with the use of the substance as documented in the application, taking into account the information submitted by interested third parties, 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): in total 41 alternatives were analysed belonging to the groups of Alkylene ethoxylates, Alkyl glucosides, Alkyl ethoxylates/isopropylates, Alkyl ethoxylates and Polysorbates.

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

[1] exact figure claimed confidential, but known to RAC

- 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 €10-100 million per year and additional benefits to society have been assessed qualitatively but have not been monetised. These additional benefits comprise health impacts resulting from the continued operation of 3 500-10 500 (the exact figure was not made public due to its confidentiality) existing (and future) Siemens Healthineers analysers. On these analysers 0.1-1 million IVD kits (the exact figure was not made public due to its confidentiality) are run yearly that help in the correct diagnosis of heart diseases, tumour markers, cancers and conditions related to fertility and diagnosis of infectious diseases disorders.

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:

- 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:[2]

- 10-100 jobs would be lost

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

Additional conditions, are proposed. These are listed in section 7 of the justification to this opinion.

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

REVIEW PERIOD

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

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

SUMMARY OF THE USE APPLIED FOR

Role of the applicant in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☒ formulator Downstream ☐ group of downstream users
Number and location of sites covered	1 000-10 000 downstream users sites in the EEA
Annual tonnage of Annex XIV substance used per site (or total for all sites)	200-400 kg/year (all sites) i.e. an average per site up to 0.02-0.4 kg/year **Note:** the quantity released is the same as the quantity used.
Functions of the Annex XIV substance.	due to its detergent properties to prevent 'non-specific binding' throughout the lifecycle of the IVD kit, from the point of production to its use at the customer site; to ensure that stability and performance of the reactive components in the IVD kit reagents
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	IVD kit reagents in analyser systems
Shortlisted alternatives discussed in the application	The applicant provided 43 alternatives belonging to the following groups: Alkylene ethoxylates, Alkyl glucosides, Alkyl ethoxylates/isopropylates, Alkyl ethoxylates and Polysorbates.
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	☐Air ☒Water ☐Soil ☐None
All endpoints listed in Annex XIV were addressed in the assessment	☒Yes ☐No if 'No' – which endpoints are not addressed
All relevant routes of exposure were	☒Yes

considered	☐No if 'No' – which routes are missing and what was the reason given
Adequate control demonstrated by applicant for the relevant endpoint	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of release used by applicant for risk characterisation	Release Water: 200-400 kg/year for a total of 1 000-10 000 downstream users' sites (i.e. an average per site of 0.02-0.4 kg/year) based on a release factor of 33-100 % (DU survey) Air: 0 g/year (Emissions to air are considered to be negligible, because of the relatively low vapour pressure of the substance of < 0.01 hPa at 20 °C) Soil: 0 g/year (direct release to soil is considered negligible)
Risk Characterisation	Environmental compartments: The applicants did not attempt to derive PNECs or RCRs. They have treated 4-tert-OPnEO as a non-threshold substance. The CSR describes how the OCs and RMMs in the Exposure Scenarios (ES) prevent or minimise releases to the environment as far as technically and practically possible
Applicant is seeking authorisation for the period of time needed to finalise substitution ('*bridging application*')	☐Yes ☒No ☐Unclear
Review period argued for by the applicant (length)	20 years
Most likely Non-Use scenario	
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	€10-100 million per year
Society's benefits of continued use	10-100 jobs lost, evaluated at €1-10 million (avoided social costs of unemployment)
Monetised health impact on workers	Not relevant
Distributional impacts if authorisation is not granted	Not quantified
Job loss impacts if authorisation is not granted	Up to 10-100 jobs would be temporarily lost in the European Union

SUMMARY OF RAC AND SEAC CONCLUSIONS[3]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

OCs and RMMs in the ES are **not** appropriate and effective in limiting the risk

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

☐Yes ☒No

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

☒Yes ☐No

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

☐Yes ☒No

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

☒Yes ☐No

2. Exposure Assessment

Releases to the environmental compartments

Air: 0
Water: 200-400 kg/year, at a total of 1 000-10 000 downstream users' sites (i.e. an average per site up to 0.02-0.4 kg/year) based on a release factor of 33-100 % (DU survey)
Soil: 0

Conclusions of RAC

RAC considers that the estimates of releases provided by the applicants are appropriate and did not identify shortcomings in the methodology used.

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

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

☒Yes ☐No

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

☐Yes ☒No

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

☒Yes ☐No

3. Risk Characterisation

Conclusions of RAC

RAC is of the view that the applicant has not demonstrated that releases to environmental compartments are prevented or minimised as far as technically and practically possible.

4. Analysis of alternatives and substitution plan[6]

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

200-400 kg/year (all sites) i.e. an average per site up to 0.02-0.4 kg/year

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

☐Yes ☒No

Has the applicant submitted a substitution plan?

☒Yes ☐No

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

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

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

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

☒Yes ☐No

Conclusions of SEAC

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

SEAC finds the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis.

Does SEAC propose any additional conditions and/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,
- SEAC's assessment of the comments received in the public consultation,
- any 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

RAC

Monitoring arrangements:

For the environment ☐Yes ☒No

SEAC

Monitoring arrangements ☐Yes ☒No

9. Recommendations for the review report

RAC

For the environment / HvE ☒Yes ☐No

SEAC

AoA ☐Yes ☒No

SP ☐Yes ☒No

SEA ☐Yes ☒No

10. Applicant comments on the draft opinion

Has the applicant commented the draft opinion?

☒Yes ☐No

Have actions been taken resulting from the analysis of the applicant's comments?

☒Yes ☐No

JUSTIFICATIONS

0. Short description of use

Siemens Healthcare Diagnostics Products GmbH (hereafter referred to as “Siemens”) applied for the use of 4-tert-OPnEO in in-vitro diagnostic (IVD) kit reagents on diagnostic analyser systems (public range: 10-100 IVD products and 10 000-50 000 relevant analysers operated across the EEA). A typical customer in a large hospital reference lab may be running 10 to 100 analysers from a particular platform, or potentially a range of analysers from different platforms. The applicant refers to this as Use 4 and the use applied for is taking place at the downstream users’ level (1 000-10 000 hospitals and laboratories). This use is in relation with Uses 1 and 2 where the applicant, Siemens, formulates IVD kits at their site in Marburg (Germany). Siemens distributes IVD products (kit reagents and wash solutions), many of which contain either Triton™ X-100, or Triton™ X-405 in typically low concentrations (in reagents manufactured by Siemens the concentration range is: 0.1-1 %) to their EEA customers. The applicant noted that a third substance (Triton™ X-705, CAS No. 9081-99-6) is also currently in use in IVD kits but the use of Triton X-705 will cease before the Sunset Date. IVD kits are typically supplied in low volumes (typically < 150 mL). All three products are based on 4-tert-octylphenol with differing degrees of ethoxylation. Individual IVD kit reagents can either be bought as an IVD kit that contains all reagents needed or individually, for example if a single reagent within a kit needs to be replenished. The number of different reagents in the IVD kit can vary. If an IVD kit contains 4-tert-OPnEO, in some cases it will be present in only one of the reagents, in other cases it will be in multiple reagents contained within that kit. The applicant noted that the number of analysers that uses IVD kits containing 4-tert-OPnEO is in the range of thousands. The applicant estimated that 200-400 kg of 4-tert-OPnEO is used per year usage in the IVD kits relevant for the use.

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

To perform an assay for a specific disease or condition, the IVD customer is essentially running a ‘ready to use’ IVD kit on a compatible analyser system. While some IVD kit reagents are concentrates and have to be pre-diluted before they can be used, no other manual steps are required apart from subjecting the sample to the test. Following a specific protocol the other IVD kit reagents are added to the sample and after that detection occurs. Many analysers can handle several assays in a row, additional core functionalities for the application of IVD kits are the automated sample processing and unique identification (e.g. by a bar code system) and the documentation of results. In some cases, different analysers are also connected with each other to measure a broad range of parameters in one sample – each by the application of a different IVD kit.

Table 1: Contributing Scenarios presented in the Use

Contributing scenario	ERC / PROC	Name of the contributing scenario
ECS1	ERC 8a	Widespread use by professional workers - Use of IVD kit reagents on diagnostic analyser systems
WCS 1	PROC 15	use of IVD Kits on diagnostic analyser systems
WCS 2	PROC 8b	collection of 4-tert-OPnEO -containing wastewater and discharge to communal waste water

WCS 3	PROC 21	collection and handling of solid waste

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

4-tert-OPnEO is used in IVD kits to achieve the following:

- to prevent 'non-specific binding' throughout the lifecycle of the IVD kit, from the point of production to its use at the customer site;
- to ensure that stability and performance of the reactive components in the IVD kit reagents (the orientation of the antibodies bound to the latex beads but also the suppression of the agglomeration of the beads itself in the kit reagent) is maintained until the IVD kit is used.

0.3. Type(s) of product(s) made with Annex XIV substance and market sector(s) likely to be affected by the authorisation

IVD kits containing 4-tert-OPnEO are used in the following diagnostic fields:

- Immunoassay;
- Clinical Chemistry;
- Haemostasis (blood coagulation);
- Plasma Protein Analytics;
- Drug-Testing;
- Cardiac; and
- Molecular Testing (detection of nucleic acids (DNA/RNA from viral, virus and bacterial sources) in blood and other bodily fluids).

In the scope of this use Triton™ X-100 and Triton X-405 are one of the components of IVD kits (range: 10-100 IVD products) that are necessary to analyse diagnostic samples in dedicated laboratory instruments (analyser) in the healthcare sector.

0.4. For upstream applications: Downstream User survey

The applicant conducted a digital, web-based survey (an invitation to participate was sent via national postal systems and email) among 1 000-10 000 relevant EU companies in their customer database, who use the Siemens products that employ 4-tert-OPnEO containing solutions. The survey was made available and released in six languages (English, French, German, Italian, Spanish and Greek). The survey contained 21 questions including those on handling of waste generated from the use of the IVD tests and the likely impact to the applicant's customers if additional RMMs are required in order to collect liquids possibly contaminated with 4-tert-OPnEO (questions covered the handling processes of analyser wastewater, wastewater volume, costs associated with waste management, alternative processes for wastewater). Overall, a range of 10-200 responses from 6 EU member states were received. The results of the survey are presented in the Use 4 AoA-SEA document.

1. Operational Conditions and Risk Management Measures

1.1. Environment

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

Waste

Solid waste:

- A small proportion of the applied 4-tert-OPnEO (applicant's assumption: < 0.1 %) adheres to solid waste like pipettes, gloves, wipes or containers, which are collected as solid laboratory waste for incineration.
- Disposable materials like gloves, lab coats, pipettes, one-time pipes, which may be contaminated with 4-tert-OPnEO, are disposed of as solid waste for incineration

Liquid waste:

- A survey conducted by the applicant showed that the majority (percentage claimed confidential but known to RAC) of the downstream users do not collect liquid wastes as biohazardous waste, and discharge it into the sewer system. The applicant has, subsequently, assumed that 100 % of their customers deal with the liquid waste in this way.
- A minority of customers collect the reagents after use, and dispose of them as hazardous waste for incineration.
- A few customers, with specific applications resulting in a high content of other hazardous compounds, collect the wastewater and dispose of it of as hazardous liquid waste for incineration

Table 2: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	Closed systems	The use of solutions containing 4-tert-OPnEO is in closed instruments, emissions to air are considered negligible.
Water	Incineration of solid waste	No residual releases assumed from solid that is collected for incineration. Release originates from down the drain disposal.
Soil	Closed systems	Direct releases to soil are not likely as the use of solutions containing 4-tert-OPnEO is in closed instruments. As the waste water leaving DU sites is discharged into a sewer and going to a municipal waste water treatment plant, 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:

- IVD kit operations are performed by healthcare staff
- Standard operating procedures
- Siemens provide training courses for workers that include handling of IVD kits and the

operation of the analyser systems. Courses also include training on the maintenance of the instrument and the disposal of consumables (the kit components and the patient samples).

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

The description of the operational conditions and risk management measures is clear for this exposure scenario.

RAC notes that the applicant assumes that all solid waste that could potentially be contaminated with 4-tert-OPnEO is collected and disposed of as waste for incineration[7]. On the other hand, and based on a survey conducted among its downstream users, the applicant assumes that the 4-tert-OPnEO containing wastewater from laboratory use, is usually discharged to the communal wastewater and treated in local waste water treatment plants (WWTPs).

The applicant noted that, according to the survey they conducted, it is clear that only a minority of customers collect the reagents after use, and dispose of them as hazardous waste for incineration and that only a few customers, with specific applications resulting in a high content of other hazardous compounds, collect the wastewater and dispose of it of as hazardous liquid waste for incineration.

The applicant pointed out that not all IVD reagents used on an IVD platform contain 4-tert-OPnEO, thus its concentration in the wastewater after use is low (< 0.01 % 4-tert-OPnEO). Based on this, the applicant concluded that, even for the platforms with the highest throughput and further separation and treatment of the 4-tert-OPnEO-containing wastewater, it is unsuitable, as a general measure, to reduce 4-tert-OPnEO-emissions to the environment from wide dispersive use.

The Applicant noted in the AoA that efforts to implement additional RMMs such as the segregation and incineration of 4-tert-OPnEO-containing wastewater would face significant technical, and practical challenges at downstream user sites, including the uncertain availability of incineration capacity for the treatment of large volumes of low calorific value waste in several Member States. Thus, the applicant concluded that a move to segregate the wastewater for all customers would lead to major financial and logistical issues for a significant proportion of healthcare institutions in the EEA. In comments to the draft opinion, the applicant provides a more detailed analysis of the logistics of shipment of wastewater to waste incineration plants. It is stated that the transport distance to such plants can be relatively long especially since for the Baltic countries, and for South-east Europe, no waste incinerator capacity was reported at all. The required transport logistics and the incineration of large volumes of wastewater causes greenhouse gas emissions. Thus the applicant considered that minimisation of emissions via phase-out of 4-tert-OPnEOs in IVD products is a far more viable and cost-effective route. The applicant expects to complete phase-out of 4-tert-OPnEO in 2041.

RAC notes that in the Analysis of Alternatives document, the applicant has assessed the technical viability of the possible risk management measures and/or operational conditions

[7] RAC notes that the conditions of use are ambiguous with respect to the treatment of solid waste. The statement that all solid waste is incinerated is an expert judgement by the applicant. In the answers to RAC question the applicant noted that the presence of potentially infectious material and chemicals often leads to a situation where solid waste has to be classified has to be classified as hazardous according to the EU-wide existing framework legislation and the respective national legislation. Thus based on the existing legislation, applicant assumed that incineration of hazardous waste is the method of choice, even if it cannot fully be excluded that some hospital waste is landfilled,

needed to ensure a complete/ partial collection of the 4-tert-OPnEO at DU sites. The applicant noted that in the survey conducted (survey sent to a range between 1 000-10 000 customers where only a small fraction of these responded) a question was asked on the possibility to implement additional RMMs at DU sites. The small number of respondents in the survey expressed concerns about the costs associated with changing their current wastewater management processes. The majority of the respondents indicated the need for structural changes, increased costs, and a reliance upon external disposal contractors, need for increased storage, and the alteration of worker routines, as the main problems. Thus, after performing its evaluation, the applicant concluded that minimisation of emissions via phase out of 4-tert-OPnEO in IVD products would be the most viable and effective route, for the following reasons:

1. The current practice of discharging diagnostic analyser wastewater to the public sewer system is in line with the EU regulatory framework for wastewater and waste management.
2. To segregate and ensure incineration of wastewater, customers would need to classify the wastewater not only as waste but specifically as 'hazardous waste' despite the fact it does not meet the criteria for classification as hazardous waste under the Waste Framework Directive.
3. Volumes of wastewater generated are very high in relation to the volume of 4-tert-OPnEO used by customers.
4. There are some significant logistical challenges in separately collecting wastewater, particularly in certain cases, e.g. a large laboratory in an old building.
5. The costs of segregating the high volume of wastewater would be significant for healthcare providers
6. It is unlikely that incineration facilities capable of dealing with the liquid waste fraction from diagnostic analysers will be available to all customer sites given the vast geographical distribution of customers across all EEA member states.
7. The environmental benefit of incinerating high volumes of wastewater to deal with relatively low volumes of 4-tert-OPnEO is a serious consideration which requires more analysis.

After considering all information and theoretical reasoning provided by the applicant on OCs and RMMs to reduce emissions, RAC is of the opinion that the applicant has **not** demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible, because no efforts are made at downstream users sites to collect liquid waste that are contaminated with 4-tert-OPnEO for adequate treatment.

RAC is of the opinion that collection of liquid waste for adequate disposal should be technically and practically possible, pointing out that in fact, some DU's actually indicated in the survey that this is feasible - and points out that direct release to the municipal sewer system cannot be considered as adequate treatment for liquid waste.

Furthermore, RAC considers the discharge of liquid wastes containing 4-tert-OPnEO residues from the DU's activities to the municipal (waste water treatment plant (WWTP is not appropriate, especially considering the quantities of 4-tert-OPnEO used and released (the applicant has estimated that the overall usage of 4-tert-OPnEO contained in the IVD kits is between 200 and 400 kg/year). At the same time, the proposed complete cessation of 4-tert-OPnEO use in 2041 cannot be considered as an appropriate risk management measure, as the releases of the substance are expected to continue for the next 20 years.

1.3. Conclusions on OCs and RMMs

Overall conclusion

OCs and RMMs in the ES are **not** appropriate and effective in limiting the risk.

Are the operational conditions and risk management measures appropriate[8] and effective[9] 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

Moderate concerns related to OCs and RMMs lead to additional conditions for authorisation presented in section 7 and to recommendations for the review report presented in section 9.

2. Exposure assessment

The applicant presented one exposure scenario (ES 1: Widespread use by professional workers - Use of IVD kit reagents on diagnostic analyser systems (ERC 8a).
Three worker contributing scenarios were presented in the CSR but were not assessed, as the scope of the CSR is limited to the environmental risk of 4-tert-OPnEO. Exposure assessment for consumers is not applicable as there are no consumer-related uses for the substance.

2.1. Environmental emissions

RAC did not evaluate the predicted environmental concentrations (PECs) provided by the applicants 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.

Water

The applicant assumed that the entirety of 4-tert-OPnEO placed on the market by Siemens is released into wastewater, which is directed to local municipal Treatment Plants (WWTP). The applicant based the assumption on the survey of its downstream users. The applicant estimated that the usage of 4-tert-OPnEO contained in the IVD kits is between 200 and 400 kg/year (exact quantity claimed confidential but known to RAC).

No measurement data from the downstream users are available.

[8] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[9] '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.

Air

No release to air is assumed, since 4-tert-OPnEO is not volatile and the formation of aerosols during use can be excluded.

Soil

IVD kits containing 4-tert-OPnEO are handled indoor in closed equipment thus direct releases to soil are not possible.

Waste water leaving DU sites is discharged into municipal sewer systems and ends up in municipal WWTPs.

Table 3: Summary of environmental emissions

Release route	**Release factor**	**Release per year** kilograms	**Release estimation method and details**
Water	33-100 %	200-400	The entire volume used by sites that do not collect their waste as hazardous is assumed to be released to water.

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 incineration of solid waste that could potentially be contaminated with 4-tert-OPnEO.

RAC points out that releases to wastewater are not minimised as effluents contaminated with 4-tert-OPnEO are disposed down the drain and discharged to the municipal WWTPs. RAC notes that there are no measured data on concentrations of 4-tert-OPnEO in wastewater disposed down the drain from the downstream users.

RAC notes that the potential for release to air is negligible as a result of the relatively low vapour pressure of 4-tert-OPnEO and the process takes places in an automated closed system which ensures a high level of containment.

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

RAC considers that the methodology for assessing the exposure is, although simplified, appropriate for the case. The release factors are based on downstream user survey, and are not likely to underestimate the exposure.

2.3. Conclusions on exposure assessment

RAC considers that the estimates for releases provided by the applicants are appropriate. RAC did not identify shortcomings in the methodology used by the applicant to estimate releases.

3. Risk characterisation

3.1. Environment

In this case, the applicant derived "latest research values" for five compartments, i.e. water, marine water, soil, and sediment and marine sediment. The applicant compared the predicted environmental concentrations (PECs) with "latest research values" for freshwater/marine aquatic/sediment organisms and soil for 4-tert-OP. RAC has not assessed this comparison as the applicant had clearly chosen a non-threshold approach in which minimisation of emissions is central and a quantitative risk assessment cannot be carried out for 4-tert-OPnEO. Furthermore at RAC-50, the Risk Assessment Committee decided, based on industry submissions contained in several applications for authorisation, that the current state of knowledge of the endocrine disrupting properties, mode(s) of action and effects of 4-tert-OPnEO in the environment is insufficient to determine a threshold.

Based on the operational conditions and risk management measures as described by the applicants in the exposure scenario, and in particular the absence of a requirement to collect liquid wastes for adequate treatment, RAC is of the view that the applicant has **not** demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects). The use applied for may result, overall, in 200-400 kg/year emissions of 4-tert-OPnEO (i.e. an average of up to 0.02-0.4 kg per site) to the environment due to the presence of 4-tert-OPnEO in the untreated waste water at the downstream user sites. This waste water is disposed down the drain and discharged to the municipal Waste Water Treatment Plants. RAC is of the opinion that untreated releases of wastewater containing 4-tert-OPnEO to the water compartment is a cause for concern and emissions to the water compartment should be minimised by implementing additional OCs and RMMs.

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 not demonstrated that releases to environmental compartments are prevented or minimised as far as technically and practically possible.

4. Analysis of Alternatives and substitution plan[10]

Under the use applied for, IVD products are used by hospitals, commercial laboratories and research centres on several Siemens Healthineers and third-party analysers. The products are

[10] 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*".

used to diagnose heart disease, tumour markers, cancers, conditions related to fertility and diagnosis of infectious diseases. The products concerned are subject to strong regulatory and quality requirements such as the ones encountered in medical sectors.

OPnEO are non-ionic surfactants used as detergents in IVD-kits, to perform an assay for a specific disease or condition. The customer is essentially running a 'ready to use' IVD-kit on a compatible analyser system. After use, the OPnEO-containing solutions are discharged to the sewage and communal WWTP.

OPnEO have to fulfil three main parameters in the IVD kits:

- Specificity (the potential of the kit to detect a certain protein with a high accuracy)
- Sensitivity (the degree to which a test does detect a target protein) and
- Stability (IVD kits are required to have a long shelf-life)

The reagents that are formulated under this use are optimised to function according to a protocol which is specific for one or more individual analyser platforms. In addition, the IVD kit reagents have been specifically designed and extensively tested to work in combination with the other components of the kit they belong to; this includes any other IVD kit reagents in the kit, any accompanying calibrator and diluent components, and also the IVD wash solutions used on the analyser with all the IVD products within an analyser platform.

The main business case in applying for authorisation is to ensure supply of products to customers performing viral test and providing life-changing result to patients in the EU and prevention of customer impact by gradually substituting OPnEO from the applicant's portfolio. To this end the applicant explains the need for an Authorisation based on allowing enough time to substitute or, to support provision of kits that are schedule to be discontinued. Siemens Marburg is acting on behalf of it downstream users and is requesting the continued use of 4-tert-OPnEO which will allow the continued use of IVD products while efforts to phase out OPE's continue.

This Use – which the applicant refers to as Use 4- has a strong connection with another use in the same application – Use 2-(formulation of IVD kit reagents).

The use applied for may result in emissions of 200-400 kg/year (the exact figure was not made public due to its confidentiality) of the substance to the environment for a total of 1 000-10 000 (the exact figure was not made public due to its confidentiality) downstream users' sites (i.e. an average per site of up to 0.02-0.4 kg/year).

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

100-1 000 kilograms

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

The Analysis of Alternatives addresses the question whether a suitable alternative for the OPnEO-component in the IVD kit reagent is available, and whether the applicant´s customers can substitute IVD kit reagents on their analyser platform by OPnEO-free IVD kits.

The application for Use 2 explains in detail the use of the substance and the width of the product portfolio concerning OPnEO. The substance is used in 50-500 products that represent 10-25 different product lines (exact figures were analysed, but were not made public due to their confidentiality).

In reaction to the inclusion of the substance on the authorisation list, the applicant launched (in 2012) an initiative to phase out the use of OPnEO across its global portfolio.

At present, as an outcome of literature studies, further desk-top analyses, internet based searches and communication with suppliers and the US-EPA, and collaboration with Universities and Institutes, the applicant presents a list of alternatives that are considered and/or are actually tested in certain IVD products.

In 2016 a study was commissioned by Siemens Healthlineers (parent company of Siemens Marburg) to focus specifically on the substitution of OPnEO in IVD kit reagents. The various branches of work conducted by the applicant resulted in a list of 43 alternative surfactants identified (Table 4-2 of AfA). The technical feasibility of these alternatives continues to be investigated by the applicant, to establish whether all required functional properties can be met. The list contains alternatives such as: Alkylene ethoxylates, Alkyl glucosides, Alkyl ethoxylates/isopropylates, Alkyl ethoxylates, Polysorbates.

Siemens Healthineers states that the main technical challenge comes from the number of formulations which contain OPnEO. These will either be subject to design change or product phase out. Based on studies performed to date, the applicant claims that most certainly a single alternative will not be a suitable substitute for every formulation.

The applicants' priorities in their research activities to substitute include: Focus on IVD products that are used often and are important for downstream users and patients, dedicate their early stage research activities to requalify the IVD kits that rely on OEM products, and phasing out of products which are requested sporadically by customers.

The applicant claims that substitution of OPnEO by the customers themselves is not a realistic option since they usually have not the R&D expertise and the R&D resources to substitute OPnEO in the IVD kit reagent. SEAC considers this plausible.

The applicant clarifies that he does not know whether OPnEO-free IVD kits are available which offer the same range of diagnostic tests, and which are designed to be used together with other components of an OPnEO-containing IVD kit. Siemens Healthineers´ portfolio includes OPnEO-free IVD kits which offer the same diagnostic tests, but the kits are designed to be used on a specific platform and/or analyser within that platform and they are not interchangeable. The IVD kits have been specifically designed and extensively tested to work together with the other components of the IVD kit they belong to. SEAC considers this explanation plausible. Therefore, the customers would need to replace their analysers or outsource at least a fraction of the diagnostic tests. Both options are described and analysed below as non-use scenarios in case the authorisation would be refused.

SEAC considers the applicant’s search methodology for shortlisting of alternatives adequate and the search for alternatives comprehensive. SEAC considers also the above shown technical feasibility criteria as relevant for concluding on shortlisting of alternatives.

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

Not applicable as no technically and economically feasible alternatives are available before the Sunset Date.

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 and its downstream user before the Sunset Date?

☐Yes ☒No

The applicant expects that, given the experience with earlier substitution processes, alternative substances may technically be feasible but not before the sunset date. The applicant also states that each product's design is unique and has to be tested fully to confirm that an alternative is acceptable. Therefore, no guarantees of success at the outset of this process can be given, even if an alternative substance has been successfully (or unsuccessfully) proven for a similar assay.

The applicant explains that it is not planning to carry out reformulations for all the affected products but only for those products that are expected to be in production/sales for a longer period of time. Therefore, substitution is planned for those products where it is deemed economically feasible.

For Use 4 in relation to manufacturing of a number of the products in scope of this AfA and for which Siemens Marburg is also applying for an Authorisation, the applicant describes a range of technical feasibility criteria that needs to be fulfilled for the substitution of an OPnEO in an IVD kit reagent. More specifically speaking, OPnEO fulfils the following technical criteria that should also be met by any alternative: 1) to be a non-ionic surfactant, to form less foam and be less affected by water hardness ions. 2) to have the right hydrophile-lipophile balance 3) to offer the right efficiency (i.e. critical micelle concentration CMC) 4) to have a cloud point well above ambient temperatures in the countries the IVD kits are shipped to. Regarding these criteria the applicant has tested the short-listed alternatives. The results are summarized in table 4.2 of the application.

In addition, OPnEO fulfil three main parameters in the IVD kits:

- Specificity (the potential of the kit to detect a certain protein with a high accuracy)
- Sensitivity (the degree to which a test does detect a target protein)
- Stability (IVD kits are required to have a long shelf-life)

The applicant stated that the concentration of OPnEO is specifically optimised so that any change on its concentration can have an effect on both the specificity and sensitivity of the entire test.

The applicant states that the feasibility testing so far has not identified a suitable alternative. The applicant expects that, given the experience with earlier substitution activities, alternatives will not be identified before the sunset date.

According to the applicant economic feasibility of an alternative substance could not be assessed since no alternative will be identified before the sun set date. It is also stated that the market prices of IVD kits reagents and analysers of Siemens Healthineers and third-party products and analysers are comparable. Therefore, in general, substitution with OPnEO-free IVD kits would be considered economically feasible, but the applicant states OPnEO-free kits with similar diagnostic ranges are unknown or could not be implemented on the Siemens

Healtineers analysers. Therefore, the customers would need to replace their analysers or outsource at least fraction of the diagnostic test. Both options are described and analysed below as non-use scenarios in case the authorisation would be refused.

No comments on alternative substances or OPnEO-free IVD kits were submitted during the public consultation.

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

The application describes the technical parameters that make each short-listed alternative a candidate for further research.

SEAC has reviewed the information provided by the applicant on each potential alternative and notes that the analysis of alternative substances is clear. SEAC, therefore, agrees with the applicant that there is no technically feasible alternative substance available by the sunset date. The assessed alternatives are still under development and more time will be needed for research and testing. SEAC however does not find it plausible that the applicant has no information about OPnEO-free IVD kit reagents supplied by competitors, but it is plausible that exchange between OPnEO kits and OPnEO free kits would be technically difficult on analyser systems since the IVD kits are optimised for each specific platform.

Regarding economic feasibility SEAC did not carry out a detailed assessment as the there are no technically feasible alternatives. SEAC notes that applicant considered the difference in market prices of the alternatives compared to OPnEO insignificant. SEAC considers that this price difference is not relevant to assess economic feasibility but that the economic feasibility of producing the IVD kits with alternative substance is more relevant. Given the claim of technical infeasibility of alternatives by the applicant, SEAC considers that the production of IVD kits would be economically infeasible.

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

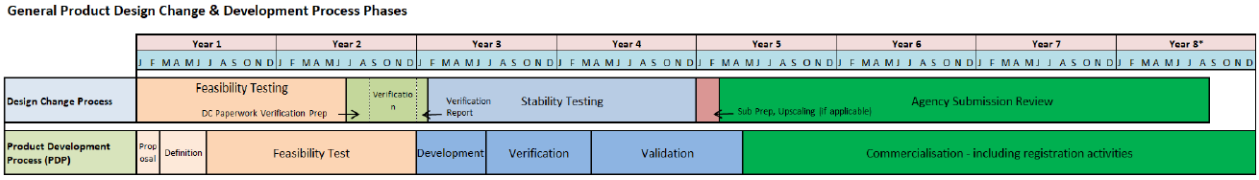
The applicant is already engaged in a substitution programme. On corporate level a substitution initiative was launched that has had some success in the wider portfolio of the applicant's products that contain 4-tert-OPnEO, the applicant is engaged in substitution activities as well for the products from the Marburg site. However it has not yet started feasibility testing in practice.

Short-listed alternatives have been assessed for technical and functional requirements. The applicant is working on a substitution initiative structured as a stepwise project, each phase has a defined timescale for implementation. In addition, the applicant has provided (confidential) information on the personal resources (FTEs) employed for substitution per IVD product group, and the current R&D status. Also (confidential) information about success or failure along the testing stages which are completed so far per IVD product and for every tested alternative is provided.

The applicant explains that the timelines for substitution of the products made at Marburg site is long and complex as they are used in a wide variety of products and each of these products requires a separate R&D project and subsequent re-registration upon successful substitution. The re-design of a product that contains OPnEO until full substitution is achieved, takes an average of 8 years according to the applicant. The applicant claims that in the case of Siemens Marburg a period, typically, of 5-12 years applies to the re-design of each formulation. The re-design of a product that does not contain itself OPnEO can be achieved in a shorter timeframe, the applicant assumes a typical timeframe of 3 years.

Figure 1 shows the phases of the process and product design change projects with typical durations for the different phases:

Figure 1: General product Design Change & Development process phases



This estimate originates from a review undertaken by MedTechEurope (of which Siemens Healthineers is a member) among its members. This timeframe is therefore considered ‘standard’ in the industry and the applicant states that other REACH Authorisation applicants may are referring to this range in the same context.

Due to the considerable amount of products and the limited amount of resources that are available, the applicant claims that substitution takes a long time (sequential testing). The main timelines are influenced by the number of formulations affected, and by the number of products that each formulation represents (i.e. one formulation may be used in more than one product, and therefore represents more documentation and registration work).

Based on studies performed to date, the applicant claims that most certainly a single alternative will not be a suitable substitute for every formulation. In sum, the applicant is planning 10-50 reformulation projects (exact figures analysed, but was not made public due to its confidentiality) for Uses 4 and 5 in sum with the main number of projects taking place for Use 4.

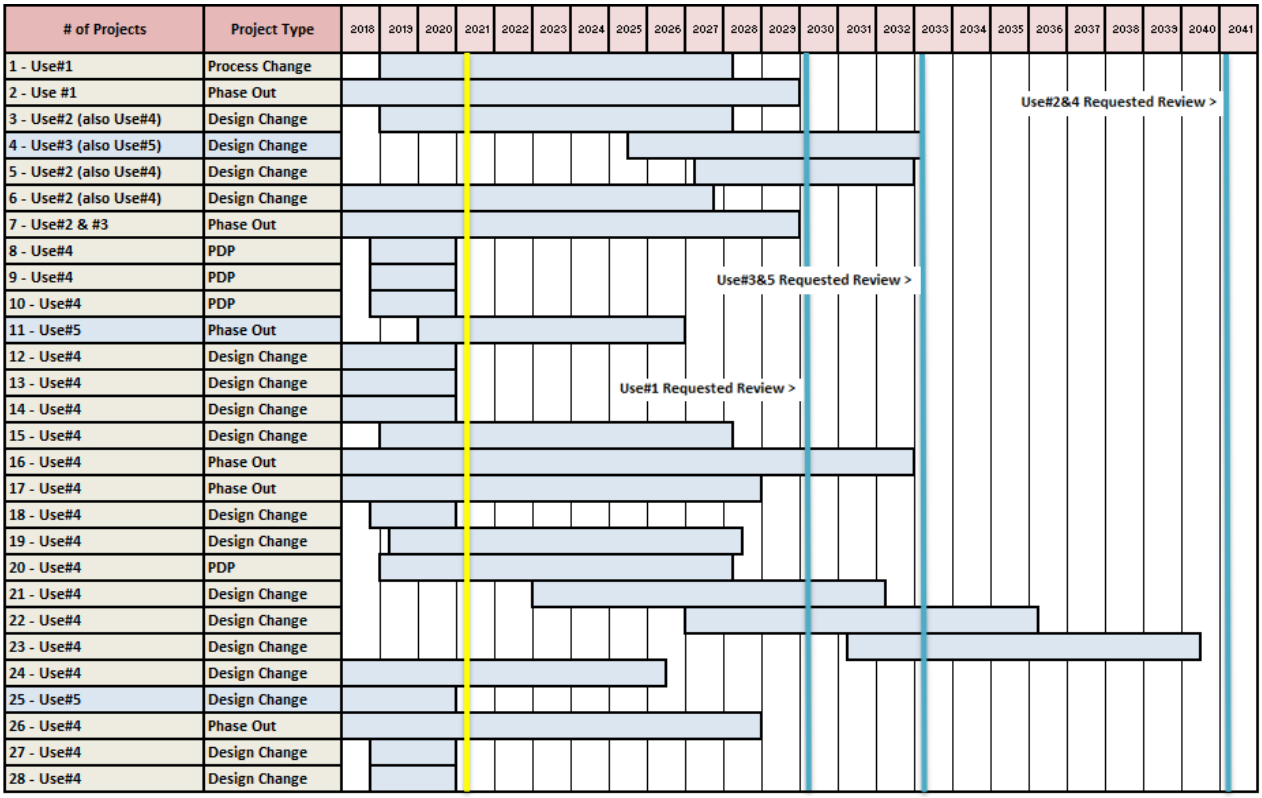
A possible alternative successfully implemented at one IVD kit does not need to fit to all IVD products, and thus needs to be tested on all kits, and on all instruments on which these kits are applied. Each stage of a design change project will typically involve resources from a wide variety range of business functions within the applicants' organisations. The regulatory re-registration of an IVD kit includes several steps and the entire re-registration process can be expected to take up to ca. 4 years.

Due to the vast amount of products and the limited amount of resources that are available, substitution is claimed to take a long time (sequential testing). The applicant argues that a 20-year review period will be needed to attain the full substitution of OPnEO for the applied use, when all the required steps that comprise the development, implementation and regulatory re-registration phases are added up and applied across the whole range of products to be reformulated for Use 4. The applicant´s main focus in their active research activities to substitute are IVD products that will have a long life-cycle, and have a high potential for emissions to the environment. Other products will be phased out.

The figure below gives an overview on the completion of the substitution for the different uses

and product groups[11]:

Figure 2: Planning and completion of on-going substitution



# of Projects	Project Type	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041
1 - Use#1	Process Change																								
2 - Use #1	Phase Out																								
3 - Use#2 (also Use#4)	Design Change																								
4 - Use#3 (also Use#5)	Design Change																								
5 - Use#2 (also Use#4)	Design Change																								
6 - Use#2 (also Use#4)	Design Change																								
7 - Use#2 & #3	Phase Out																								
8 - Use#4	PDP																								
9 - Use#4	PDP																								
10 - Use#4	PDP																								
11 - Use#5	Phase Out																								
12 - Use#4	Design Change																								
13 - Use#4	Design Change																								
14 - Use#4	Design Change																								
15 - Use#4	Design Change																								
16 - Use#4	Phase Out																								
17 - Use#4	Phase Out																								
18 - Use#4	Design Change																								
19 - Use#4	Design Change																								
20 - Use#4	PDP																								
21 - Use#4	Design Change																								
22 - Use#4	Design Change																								
23 - Use#4	Design Change																								
24 - Use#4	Design Change																								
25 - Use#5	Design Change																								
26 - Use#4	Phase Out																								
27 - Use#4	Design Change																								
28 - Use#4	Design Change																								

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

The applicant provided stepwise timelines for achieving certain steps in their substitution plan with an overall goal to finish all activities and replace OPnEO across all IVD kits before the end of the year 2040. SEAC recognizes that for Use 4 many reformulations projects needs to take place (see Figure 2). However, SEAC notes that there is a lack of certainty that the analysis of alternatives and substitution plan (including regulatory approvals) justifies a 20-year review period. A large fraction of the sum of the reformulation projects is linked to a specific platform, and it is not fully clear why no transfer of test results gathered between IVD products would be possible to save testing efforts.

Furthermore, SEAC is of the opinion that once an alternative substance has been characterized and validated for the six products, the product development/registration steps for each of the six products could be initiated within a much shorter timeline than currently planned by the applicant. SEAC takes note of the applicant's argument that simultaneous substitution of the six products would not be feasible due to resources and capacity constraints. However, SEAC is of the opinion that resource efficiency improvements during the substitution process may happen when experience is gained with the substitution of the first product. Therefore, it could be that the substitution of the other products would require fewer resources and be initiated.

Conclusions of SEAC

SEAC concurs with the applicant that there is currently no technically feasible alternative.

[11] PDP = Product Development Process.

Due to high performance requirements 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.

SEAC however, does not find the substitution plan in its sequential structure fully credible Resource efficiency improvements during the Design change processes may arise when experience is gained with the substitution of the first product which were not sufficiently reflected in the substitution plan. SEAC therefore considers that a very long substitution period of 20 years is not well justified. Therefore, SEAC recommends a 12-year review period.

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

SEAC's is of the opinion that the applicants convincingly demonstrates that technically feasible alternatives will not become available to the applicants before the sunset date.

Due to high performance requirements 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.

SEAC concludes that the analysis of alternatives is clear in its description and scope and sufficiently detailed to conclude on the short-list derivation of alternatives as well as their suitability in the context of the use applied for. The applicant described the use applied for in detail, as well as the key technical requirements associated with a viable alternative. In presenting their substitution plan, specific timelines for completion as well as the expected outcome resulting from each phase were outlined by the applicants.

No comments were received during the public consultation on alternatives.

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

4-tert-OPnEO was included on Annex XIV of REACH due to the environmental impacts of its degradation products. As a result, impacts on human health are not included in the context of this application.

Due to the use of IVD kit reagents, releases to the aquatic environment and to the soil arise. A small fraction of the 4-tert-OPnEO is contained in solid waste like pipettes, gloves, wipes or containers which is collected and incinerated. This volume is considered small but could not be quantified by the applicant. The use of 4-tert-OPnEO results into releases of 4-tert-OPnEO to waste water, and further to the local municipal sewage treatment plants. The applicant states that only a few customers will collect the reagents after use and dispose of it as waste. But, the amount not released via wastewater cannot be quantified. Therefore, it is conservatively assumed by the applicant, that 100 % of the consumed IVD kit reagents and the contained 4-tert-OPnEO is discharged to wastewater.

The applicants estimate that under the requested review period of 20 years for Use 4 (2021-2040) exposure to the aquatic environment will be 200-400 kg annually over the requested

review period (exact figures analysed, but were not made public due to its confidentiality).

SEAC takes note of RAC's conclusion that the OC and RMM are not effective in minimising the releases and RAC's consequent advice to impose additional conditions detailing out the need for additional risk management measures. SEAC takes note of the analysis of the applicant on additional risk management measures.

For the implementation of a segregation system to collect the fraction of wastewater from 4-tert-OPnEO containing reagents and wash solutions, a drainage network and a waste collection system has to be installed at the site of each customer. The applicant provides indicative numbers for implementation and incineration costs of collected wastewater per customer.

The installation costs will depend on the number of analyser platforms that each site has installed, the available space for storage of waste, the age of the facility, the location of a laboratory, etc. This analysis details out that additional RMM would be implemented at a high cost with customers facing costs of incineration at €600-1 000 per tonne of waste water plus installation costs of segregation systems, the cost of which can range between €20 000-40 000.

The RMM would avoid 4-tert-OPnEO releases to the water compartment of 200-400 kg/year for a total of 1 000-10 000 downstream users' sites. With the total number of sites in the range of 1 000-10 000, total one off costs ranging from €20-400 million would arise. At an average use of 0.02-0.4 kg per site, this would result in an annual operational cost of €1 500-€30 000 per year per site. The applicant also mentions as a drawback of this RMM, the environmental impact of CO_2 emissions due to the incineration of wastewater.

In the comments to the draft opinion, the applicant presents a more detailed estimation of the generated wastewater given the stock of Siemens Healthineers analyser systems installed in EU in 2019 covering wastewater volumes generated by Uses 4 and 5. The detailed calculation are claimed confidential, but are available to the SEAC rapporteurs. The incineration costs are estimated to be about €600 000 per kg 4-tert-OPnEO emissions prevented, the estimation is based on:

- **Number of analysers** installed in EEA, SEAC considers this estimation be plausible given the numbers of installed analysers in 2017 and the forecasted sales of Siemens Healthineers analysers which were already are presented in the application for authorisation.
- **Operating hours of analysers** will depend on the type of the laboratory: Hospital, commercial lab, R&D lab. The assumed average operation hours for analysers of 16 h per day seem plausible, the figure is based on labs operating 16 h/day (many laboratories will operate 24 h, others only 8 h), 270 days/year.
- The applied **average cost of wastewater incineration** of €900 per ton are also plausible, the figure is based on actual cost of waste management companies (reported by the applicant to be between €600-1 200 per ton of wastewater).
- The presented **amount of wastewater consumed** per hour per analyser could not be verified fully. The figures from the downstream user survey about annually produced wastewater show lower figures. SEAC notes that the number of responses to the customers' survey were quite low given the number of invited customers. Also a fraction of the customers already collect and send wastewater to a WWTP.

SEAC questioned the applicant on why that volume of annual wastewater volume presented in the customer survey is much lower than annual wastewater volume per analyser given in the calculation sheet (difference of a factor 10). The applicant explained that it had made an effort to provide a balanced and reasonable view taking into account the many variables across the

customer base (i.e. number of analysers run, hours/day used, whether downtime/maintenance happens out of hours, working days/year etc). This led the applicant to conclude that an average of 30 tonnes/year would represent a majority of the downstream users and creates a realistic scenario for the calculation of costs. The applicant explained further that even though he is aware that for some customers this is an overestimation, on the other hand it is very obvious that in some cases this will be a significant underestimation as the responses indicating a very high emission of wastewater show. SEAC accepts this explanation.

SEAC concludes that some overestimation of the presented incineration costs cannot be excluded. But SEAC recognizes that the magnitude of the incineration costs as estimated by the applicant is plausible.

The applicant refers to a study by the Vrije Universiteit Amsterdam (VU, 2015) assessing the costs of reducing releases of PBT/vPvB substances[12] to characterize the wastewater incineration costs as disproportionate. Based on the assessment, VU suggested that there is a 'grey zone' of €1 000-50 000/kg in which the measures to reduce the use, presence or emission of PBTs may be prohibitive from a cost-effectiveness point of view. SEAC does not consider this threshold relevant, since the costs related to reducing PBT/vPvB substances are not directly applicable to substances with endocrine disrupting properties for the environment and since the €/kg range derived in the VU (2015) study cannot be interpreted as social cost of 4-tert-OPnEO emission.

5.2. Benefits of continued use

Non-use scenario

The applicant has assessed five non-use scenarios:

- Replacement of the 4-tert-OPnEO-containing component of an IVD product (the IVD kit reagent) with a 4-tert-OPnEO-free component.
- Replacement 4-tert-OPnEO-containing IVD kits with analyser-compatible 4-tert-OPnEO -free IVD kits.
- Purchase of new analysers that only use 4-tert-OPnEO -free IVD kit reagents or IVD wash solutions
- Outsourcing of the tests that depend on 4-tert-OPnEO -containing IVD products to a third party
- Cessation of diagnostic operations which involve the use of 4-tert-OPnEO -containing IVD products.

As was shown in the Analysis of Alternatives no technically suitable alternatives will be available before the sun set date. Even if an alternative was identified during the time needed for implementation and re-approval of the alternative substance, would require a temporary shot down in operations of such an extent that the amount of customers that would be irrevocable lost would render sudden immediate substitution to be economically not feasible

According to the applicant the Siemens Healthineers IVD kits are designed for a specific product platform and specific analysers. An exchange with other kits of the Siemens Healthineers portfolio is therefore technically not possible. Some specific analysers are designed as open channel systems (different to closed channel systems) on which third-party IVD kits can be

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

applied. On these analyser systems in principle, 4-tert-OPnEO-free IVD kits with the same diagnostic test capabilities can be used. The applicant states that it cannot be confirmed that such alternatives are available on the market. However, in case alternatives could be identified for adaptation, testing, and validation of the new IVD kit about 6-24 months would be needed and during this period no test services can be provided by the laboratories. In sum, the applicant has dismissed this scenario as the availability of third-party IVD kits with similar performance is considered very unlikely, or the non-availability of disease diagnostic during **test kit replacement** would not be acceptable for Siemens Healthineers customers.

The **shift to alternative analysers** on which 4-tert-OPnEO -free IVD kits with the same performance can be applied would raise significant costs. These costs comprise the additional capital costs for prematurely switching to third-platform analysers before end-of life expectancy of the existing analyser stock, profit losses during non-availability of test diagnostics for commercial laboratories, and costs of outsourcing for tests which do not require instantaneous results. This option is considered as the **most likely non-use scenario** since it would allow to deliver diagnostic testing at least in the longer-term.

The applicant considers **outsourcing** not a feasible option since the additional test capacity is not available in the EU what was also confirmed by customer surveys. It was also considered unlikely that 4-tert-OPnEO-free IVD kits with the same range of diagnostic tests are available in the EU. Outsourcing outside the EU would not be practical due to the long turnaround times, and thus only for tests which do not require instantaneous results.

Stop of testing until 4-tert-OPnEO -free technology has been developed would include an increased burden for the patients because of undiagnosed disease associated with increased morbidity and mortality for the patients and was therefore excluded.

In sum, SEAC finds the non-use scenarios discussed adequate with a focus on duration and consequences of disruption of supply of test diagnostics for the patients. As most likely non-use scenario the purchase of new analysers on which 4-tert-OPnEO -free IVD kits can be used was selected given such analysers were available on the market.

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

- the use would be substituted by market actors operating inside the EU

The applicant identified as the most likely non-use scenario the purchase of new analysers on which 4-tert-OPnEO -free IVD kits can be used. However, the applicant underlines that he does not has sufficient information which confirm that such analysers are available on the market.

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

- up to 10-100 jobs would be temporarily lost in the European Union

Economic impacts of continued use

The applicant assesses three main categories of impacts: economic impacts on the customers (hospitals, commercial and publicly owned laboratories), the applicant, the applicant´s parent company, and its suppliers, health impacts on the care providers and patients, and employment-related impacts on employees along the supply chain.

Economic impacts

The Siemens Marburg **customers** (hospitals, laboratories) will be negatively affected by non-availability of IVD kit reagents. As non-use scenario prematurely switching to third-party platform analysers using 4-tert-OPnEO-independent assays was assumed. Given the average age of the analyser type on which the IVD kits in the scope of Use 4 are applied, and the remaining life time of the analysers, the capital costs of premature replacement were calculated in the range of €10-100 million for Use 4 (NPV 2017; exact figures analysed, but was not made public due to its confidentiality).

In addition, the replacement costs of new analysers (2018-2020) based on a sales projection were estimated to be in the range of €10-100 million. Because there is overlap in the Uses 4, and 5 applied simple aggregation of the costs for Uses 4 and 5 will overestimate the total replacement costs of both uses. Profit losses, tendering costs, potential outsourcing costs, and validation costs which may arise during the time needed for replacement were not quantified. The applicant states that these figures understate the real economic impact since the analysis assumes that 4-tert-OPnEO -independent IVD kits and analysers are available and the replacement will take place in a relatively short time.

The economic impacts for the applicant covers direct impacts for Siemens Marburg, and the parent company, Siemens Healthineers, with production facilities located in the USA and the EU which is also a provider of the analysers and IVD kit reagents.

A refused authorisation for the **Siemens Marburg** customers and a switching to third-party analysers would cause a stop of sales of IVD kit reagents (Use 2), and consequently shut down of production of these IVD kits. The applicant bases the direct economic impact of shutdown on the profit losses over the 20-year requested review period. For the IVD kit reagents losses of future profits in the range of €10-100 million are calculated (NPV in 2017, discount rate 4 %; exact figure analysed, but was not made public due to its confidentiality).

In addition, **Siemens Healthineers** will lose sales of IVD kits to the EU manufactured in USA and the EU. But for estimation of profit losses only the IVD kits produced in the EU were taken into account in the range of €0.1-1 billion (exact figures analysed, but were not made public due to its confidentiality) following the approach for the geographical scope of SEA in AfA (SEAC 2016).

For **Siemens Healthineers** also the profits from sales of analyses on which these OPE-dependent IVD kits are applied will be at risk in case of non-authorisation. The applicant estimates profit losses to be in the range of €10-100 million for Use 3 at maximum. In response to a SEAC question, the applicant clarified that since on these analysers in principle also other IVD kits can be run not all customers will refrain from buying theses analysers. Since the operating of the analysers is dependent on their ability to run different types of IVD kits for any estimation of profit losses assumptions have to be taken to distribute the profit losses over the different Uses 4 and 5. On request the applicant clarified that estimated profit losses depend on past sales per analyser type, and that sales of analyser types on which Use 1 IVD kits can be operated are the most frequented, followed by Use 2 and Use 3 (the exact numbers for the use dependent profit shares were analysed but were not made public due to their confidentiality). Furthermore, differences in profit margins between analyser types were ignored. SEAC considers the assumptions taken plausible, but notes that the figures can only provide an order of magnitude for the profit losses.

OEM-manufactures for Siemens Healthineers located in the EU may also face sales and profit

losses. The applicant does not have information for quantification of these losses.

The applicant mentions that sales and profit losses for Siemens' **suppliers** located in the EU will arise but which could not quantified.

Health impacts

The applicant's products provide significant support for delivering test results which can be life-saving or life-changing for patients. These IVD kits can support the early diagnosis of certain cancers, diagnosis and treatment of kidney and renal diseases, detection of viruses etc. Any supply disruption to the applicant's reagents would have an impact on hospitals and laboratories that will ultimately be passed on to patients which will be adversely affected by an increased disease burden.

Data provided by the applicant shows that IVD kit reagents linked to Use 4 in the range of 0.1-1 million were sold in the EU in 2017. This translates into tests in the range of 0.1-1 billion which are within the scope of Use 4. SEAC agrees that the disruption in supply of the wash-solution would negatively impact a significant number of patients each year associated with an increased morbidity and mortality.

Social impacts

Since 4-tert-OPnEO -dependent operations at **Siemens Marburg** relate only to a small share of the overall profits of Siemens Marburg the share of employees at risk of unemployment are estimated as the profit share of the respective use times number of full-time employees (range: 1 000-10 000; exact figure analysed, but was not made public due to its confidentiality).

The applicant estimates job losses in the range of 10-100 full-time workers for Use 4 at Siemens Marburg, and at the European Distribution Centre for IVD kits. As described above stopping 4-tert-OPnEO activities (e.g. manufacturing the IVD kit reagents) may also reduce the sales of 4-tert-OPnEO independent products that are linked to specific analysers and 4-tert-OPnEO products. Therefore, the employment losses can be even be larger.

The calculation of social impacts follows the approach outlined in the SEAC paper on the Social Cost of Unemployment (ECHA 2016). Social costs of unemployment are calculated to be in the range of €1-10 million (exact figure exact figures analysed, but were not made public due to its confidentiality).

As a worst-case social costs of shut-down of operations at Siemens Marburg and the sister company are calculated to be in the range of €0.1-1 billion (exact figure analysed, but was not made public due to its confidentiality) (range of job losses: 1 000-10 000) (exact figure analysed, but was not made public due to its confidentiality).

Wider economic impacts

The applicant has qualitatively described the impact on the competitiveness level in the EU of a refused authorisation for manufacturing of IVD kits by Siemens Marburg. The impacts are critically depending on whether competitors are able to supply a similar range of assays without using 4-tert-OPnEO. But the applicant states that he has no information on the dependence of competitors' IVD kits from 4-tert-OPnEO, but knows that some competitors will submit AfAs. Therefore, the applicant cannot conclude on the impacts for the intra-EU competitiveness level of a refused authorisation. Also a conclusion on EU competitiveness with non EU-made IVD kits is not possible, since dependence of competitors' IVD kits from 4-tert-OPnEO, and 4-tert-OPnEO-content in imported kits is not known.

Table 4: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts [Present Value, in € million] [13]
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	(2021-2040) Siemens Marburg: €10-100 Siemens Healthineers: IVD kits: €100-1 000 Analysers: €100-€1 000 Total sum: €100-€1 000 Per average year: Siemens Marburg: €1-10 Siemens Healthineers: IVD kits: €10-100 Analysers: €1-10 Total sum: €10-100 (based on 1 year profit loss)
1.2 Avoided profit loss due to ceasing the use applied for[14]	Not Available
1.3 Avoided relocation or closure cost	Not Available
1.4 Avoided residual value of capital	Not Available
1.5 Avoided additional cost for transportation, quality testing, etc.	Not Available
Sum of benefits to the applicant and / or their supply chain	€10-100 (based on 1 year profit loss)
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[15]	10-100 jobs, evaluated at €1-10
2.2 Foregone spill-over impact on surplus of alternative producers	Not Available
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	1.: €10-100 2.: €10-100 Sum: €10-100
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	Not Available
Sum of impacts of continuation of the use applied for	€10-100
3. Aggregated socio-economic benefits (1+2)	€10-100 (based on 1 year profit loss)

5.3. Combined assessment of impacts

The applicant has provided estimates of the monetised costs of the non-use scenario, which include lost profits for Siemens Marburg, the parent company Siemens Healthineers, and capital costs for Siemens Marburg´ customers, as well as social costs of unemployment over

[13] Totals and subtotals in the table are based on the confidential figures, so the public ranges reported may not result of adding up the public ranges of the component figures.
[14] Profit losses to be counted in only for the first year, see SEAC note on economic surplus changes (not yet available).
[15] Job losses to be accounted for only for the arithmetic mean period of unemployment in the concerned region/country as outlined in the SEAC paper on the valuation of job losses (See The social cost of unemployment and Valuing the social costs of job losses in applications for authorisation).

the requested 20-year review period. The exact estimates are considered confidential by the applicant; however, the cost would be in the range of €0.1-1 billion for a 20-year review period, and €10-100 million for one year (exact figures analysed, but were not made public due to its confidentiality).

According to the applicant these estimates can be considered conservative especially since health impacts of non-available tests for diagnosis and treatment of patients are not quantified, and thus not included. Furthermore, profits losses from sales of 4-tert-OPnEO-dependent IVD kit reagents (Siemens Marburg) and analysers relevant to Use 4 (Siemens Healtineers) to non-EU customers were not taken into account.

The applicant also presents a cost-effectiveness ratio for a given reference year (taken to be 2021). In the case of the cost effectiveness ratio, the monetised impact for one year is divided by the expected substance release in one year. The resulting cost-effectiveness ratio is between €0.003 and €0.02 million per kg of 4-tert-OPnEO released.

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

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits [present value, in € million]	€10-100 quantified avoided foregone profits, + €1-10 avoided social costs of unemployment	Monetised excess risks to workers directly exposed in the use applied for [annualised to € million per year]	Not applicable
Quantified impacts of the continuation of the SVHC use applied for on other actors	€10-100 million avoided costs for shifting to new analyser systems for hospitals and laboratories	Monetised excess risks to the general population and indirectly exposed workers [annualised to € million per year]	Not applicable
Additional qualitatively assessed impacts	Possible avoided impacts on hospitals due to the lack of availability of the applicant's IVD assays (over and above what could be claimed from the applicant).	Additional qualitatively assessed risks	Risks associated with the direct release of 200-400 kg per year
Aggregated socio-economic benefits [for quantified impacts: present value, in € million]	**€10-100 avoided foregone profits for the first year** **+ €10-100 avoided costs for shifting to new analyser systems for hospitals and laboratories** **+ €1-10 avoided**	**Aggregated excess risk [annualised to € million per year and main qualitatively assessed risks]**	Risks associated with the direct release of 200-400 kg per year

	social costs of unemployment		

Table 6: Cost of non-use per kg

Total cost (€)	€10-100 million
Total emissions (kg)	200-400
Ratio (€/kg) over the review period (assuming 200-400 kg per year over a 12 year Review period), differences may exist due to rounding.	€0.003-0.02 million/kg

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg per year, based on Table 5
3. "Ratio" = Total cost/Total emissions

* For calculation of the range max (min) total cost were divided by min (max) total emissions per year.

5.4. SEAC's view on Socio-economic analysis

SEAC considers the applicant's non-use scenario, which assumes that **Customers** (end-users) switch to new analysers on which 4-tert-OPnEO -free IVD kits can be used justified. SEAC considers substitution of the 4-tert-OPnEO component until sunset date not possible as was shown above. Regarding the specificity of IVD kit reagents used on Siemens analysers it seems plausible that some IVD kits are designed for specific types of analyses (closed channel analysers) and cannot be replaced by other third-party kits. On request the applicant clarified that this specificity is not dependent on whether the kits contains 4-tert-OPnEO or not. However, for the share of open channel analyser systems substitution in principle is technically possible but affording since substantial testing and documentation would need to be done by third-party IVD manufacturers or the customers. The applicant underlines that the analyser system, the IVD kit reagent and the wash-solution are designed to work together which each other. Thus no part of the system can be changed without having an impact on the test performance.

SEAC agrees that outsourcing of diagnostic testing can only be considered as a practical and affordable solution over the short-term during the time needed to install and implement a new third-party analyser system (about 6 months), and only for tests which do not require instantaneous results. Nevertheless, for the majority of tests this would not be feasible. SEAC finds it plausible that the shift to new analyser platforms may in principle provide new opportunities for the customers to select 4-tert-OPnEO -free IVD with similar testing capabilities, although SEAC notes the uncertainties about the availability of suitable 4-tert-OPnEO -free IVD kits. In a response to SEAC question, the applicant underlines that he considers the assumption of available 4-tert-OPnEO -free kits as optimistic since he does not have information on whether competitors use 4-tert-OPnEO in their products or not. However, this assumption allows quantifying impacts of non-use without overestimating them. SEAC finds this plausible.

SEAC considers the described steps and related costs of switching to new analysers systems all relevant. The assumptions taken are conservative (e.g. constant real analyser prices), and will underestimate the costs (validation costs and profit losses during implementation not

quantified). Significant costs for the customers would arise. But SEAC notes that the cost calculation may entail some double counting since the switching costs arise for the majority of analysers for both Uses 4 and 5 simultaneously. Therefore, SEAC considers the cost estimate provided by the applicant as uncertain. But SEAC recognizes the losses to provide an indication of the social losses of non-availability of specific IVD kits for the customers.

SEAC considers plausible that that the **customers** of Siemens Marburg IVD kit reagents may be induced to replace Siemens Healthineers´ analysers before end of service life in case specific analysers can only be operated with 4-tert-OPnEO -depended IVD kit reagents. The described steps and related costs of switching to a new analyser are all considered as relevant. The assumptions taken are conservative (e.g. constant real analyser prices, and will underestimate the costs (validation costs and profit losses during implementation not quantified). Especially the additional capital would involve significant costs for the customers. However, Siemens Marburg highlights that it does not have the information about the dependence of the third-party analysers on 4-tert-OPnEO -depending reagents of competitors or plans of competitors for 4-tert-OPnEO substitution or authorisation. Therefore, SEAC considers plausible that customers have to bear costs to adapt to the non-availability of the 4-tert-OPnEO -dependent IVD kit reagents, but considers the cost estimate provided by the applicant as uncertain. SEAC recognizes the losses to provide an indication of the social losses of non-availability of specific IVD kits for the customers.

For **Siemens Marburg** the main economic impact is foregone profits due ceasing production of IVD kit reagents (2021-2040). SEAC notes that the correct procedure for discounting was applied and the adjustment of price levels to the base year was correct. However, SEAC notes the difficulties inherent in forecasting sales over long periods: the projected growth per year of IVD kit sales (varying positive and negative figures) is part of the business plan of Siemens Healthineers. SEAC considers the growth rates as moderate, but notes that the loss could be regained gradually under the non-use scenario as activities/resources are redeployed to areas unaffected by non-authorisation.

SEAC considers that changes in profits are a relevant measure of changes in producer surplus and appropriate to monetising the welfare implications of continued use. However, changes in profits made by the applicant do not necessarily reflect changes in economic surplus across the EU economy. SEAC requested further information on the performance of the competitors IVD kit reagents in the EU. The applicant underlines that he does not have information about whether competitors would be able to offer IVD kit reagents independent from use of 4-tert-OPnEO, but covering the same range of diseases. Also no information is available about competitors' production capacities. Therefore, the response provided does not clarify this item, and it is uncertain whether its direct competitors would take over the abandoned market shares in the non-use scenario. Therefore, to avoid possible overestimation of surplus losses, SEAC assumes that the competitors would be able to take-over the applicants market shares which would likely compensate in the long-run for the surplus losses made by the applicant. Therefore, SEAC does not consider it appropriate to use the profit loss incurred by Siemens Marburg over 20 years but notes that even if one considered only one year of profit loss as the economic impact of non-authorisation on the applicant, this would still be in the range €1-10 million.

It is plausible for SEAC that the parent company **Siemens Healthineers** and the OEM-manufacturers may have to face sales losses for analysers and IVD kits linked to Use 4. The applicant clarified that the profits generated by the production facilities in the EU accrue to Siemens Healthineers in the EU. However, it cannot be excluded at least parts of the profit losses of the parent company will be distributional if sales of alternative analysers increase, and at least partly compensate for the profit loss. Therefore, again SEAC does not consider it

appropriate to use the profit loss incurred by Siemens Healthineers over 20 years but notes that even if one considered only one year of profit loss as the economic impact of non-authorisation on the applicant, this would still be in the range €10-100 million for IVD kits, and €1-10 million for the analysers.

SEAC considers that the most plausible non-use scenario would result in unemployment of some of the applicant's workers, and at the European Distribution centre Duisburg. In general, SEAC considers the applicant's approach to assessing the social impacts of unemployment to be appropriate, but the input values for unemployment duration and salary are not sufficiently specific to Siemens Marburg´s situation, since representing average values for Germany. SEAC has requested further information on skills and competence level of staff involved for Use 4, and their salaries compared to the German average. The applicant clarified that average salary of the staff employed at Siemens Marburg is above the German average value. Given the salary specific to the applicant's staff the calculation of social costs was updated without having an impact on the ranges of social costs provided. In his response, the applicant underlines that the job losses represent an underestimate due to the knock-on effects on sales of other IVD kits. SEAC finds this plausible.

SEAC considers that the qualitative descriptions of the tests for the diagnosis of various diseases provided by the applicant to demonstrate the medial value of these products for the patients. Since the IVD kit reagents would be needed to perform about 0.1-1 billion tests annually (exact figure analysed, but was not made public due to its confidentiality). SEAC concludes that a large number of patients would be affected in the non-use scenario with potentially very adverse consequences since delayed diagnosis could increase mortality and treatment costs.

SEAC considers plausible that cost-effectiveness ratio which gives a value of between €0.03 million and €0.02 million per kg released can be seen as conservative as it does not take into account the medical impacts, which would significantly increase the benefits of continued use and, in turn, cost-effectiveness.

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,
- additional information provided by the applicant,
- RAC's assessment of the risks to the environment.

SEAC takes note of the conclusion of RAC that the applicant has demonstrated that releases to environmental compartments have not been prevented or minimised as far as technically and practically possible, with the view to minimising the likelihood of adverse effects.

The use applied for may result in emissions of 200-400 kg/year of the substance to the environment for a total of 1 000-10 000 (the exact figure was not made public due to its confidentiality) downstream users' sites (i.e. an average per site up to 0.02-0.4 kg/year). SEAC takes into account the benefits of continued use to the applicant, and the patients benefitting from products associated with the use applied for. These additional benefits comprise health impacts resulting from the continued operation of 3 500-10 500 (the exact figure was not

made public due to its confidentiality) existing (and future) Siemens Healthineers analysers that use 0.1-1 million IVD (the exact figure was not made public due to its confidentiality) kits that help in the correct diagnosis heart diseases, tumour markers, cancers and conditions related to fertility and diagnosis of infectious diseases disorders.

SEAC notes also that the applicant does not have information about the ability of competitors to provide IVD kit reagents with similar diagnostic test capabilities or about their production capacities. Therefore, some of the applicant´s profit losses may be of distributional nature and do not represent a loss of social surplus. The competitors and customers of Siemens Marburg would need time to react to the non-availability of the test kits, should an authorisation not be granted. Even if one considered only one year of profit loss as the economic impact of non-authorisation, this would be in the range of €10-100 million for this use.

SEAC takes note of RAC's conclusion on that the OC and RMM are not effective in minimising the releases and RAC consequent advice to impose additional conditions detailing out the need for additional risk management measures. SEAC takes note of the analysis of the applicant on additional risk management measures. The application explains the need what investment would be needed to achieve minimisation, this would result in an annual operational cost of €1 500-€30 000 per year per site.

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 gave no advice on the length of the review period.

6.2. Substitution and socio-economic considerations

The applicants consider that their analysis of alternatives and substitution plan provides sufficient justification for a longer than 12-year review period, and requests a review period of 20 years in order to develop, implement and validate alternatives for the use applied for.

In identifying the proposed review period SEAC took note of the following considerations:

- No direct emission to the soil from 4-tert-OPnEO will take place since all contaminated solid waste is collected and incinerated. Emissions to the aquatic environment are in the order of 100-1 000 per year.
- 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. The applicant's impact assessment was considered by SEAC to provide robust conclusions in this respect.

- SEAC finds it credible that it would not be possible for the applicant to substitute within a normal review period but that the applicant has not demonstrated sufficiently such a transition will be possible within their requested review period.
- SEAC concurs with the applicant that there is currently no technically feasible alternative.
- Due to high performance requirements and the regulatory approval process, SEAC finds it credible that it would not be possible for the applicant to substitute within a normal (seven year) review period.
- SEAC, however, does not see sufficient basis to grant a 20-year review period. Following the guidelines set out on the CARACAL paper on the criteria to consider for a longer than 12 years review period, the criterion of negligible emissions to the environment cannot be considered to be fulfilled. Furthermore, this case does not fall within any of the examples laid out in the CARACAL's paper non exhaustive list, since the substance is not a source of a biologically essential inorganic micronutrient for human, plant, animal or microbial cells and neither is the substance irreplaceable due its atomic properties. The substance is neither used in the production of spare parts, nor is it used in the defence sector, nor has the substance been authorised in accordance with other EU legislation.

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

7. Proposed additional conditions for the authorisation

Were additional conditions[16] proposed for the authorisation?

☒ Yes

☐ No

7.1 Description

RAC

Proposed additional conditions

o In addition to all solid waste containing 4-tert-OPnEO, all liquid waste containing the substance shall be collected for adequate treatment. The treatment shall minimise releases to environmental compartments as far as technically and practically possible. Release into the municipal sewer system or to surface waters is not considered to be adequate treatment.

SEAC

Proposed additional conditions

None proposed

[16] 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.

7.2. Justification

The applicant states that collecting liquid waste for incineration implies an additional administrative burden and costs for the end-users especially considering that there is no requirement in the ES for downstream users to collect liquid wastes for adequate treatment (e.g. for incineration). Moreover, the applicant may be placed at a commercial disadvantage if only their downstream users are required to collect their liquid waste for incineration. After considering all information and theoretical reasoning provided by the applicant on OCs and RMMs to reduce emissions, RAC is of the opinion that the applicant has not demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible, because no efforts are made to collect liquid waste that is contaminated with 4-tert-OPnEO for adequate treatment at downstream users sites. Although collecting liquid waste for adequate treatment (e.g., incineration) might imply an additional administrative burden and costs for downstream users and the applicant, RAC concluded that a condition to collect liquid waste for adequate treatment should be technically and practically possible.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[17] proposed for the authorisation?

☐ Yes

☒ No

8.1. Description

8.2 Justification

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1 Description

In case a review report is submitted, the applicant shall report on a new representative survey of their downstream users about their efforts to collect all liquid waste for adequate treatment, and which treatment methods are applied (e.g., incineration).

[17] 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.

9.2 Justifications

In line with the proposed additional condition for the authorisation (see Section 7), a new representative downstream user survey will allow RAC to evaluate the collection and treatment of liquid waste and any remaining releases to environmental compartments.

10. Comments on the draft final opinion

Did the applicant provide comments on the draft final opinion?

☒ Yes

☐ No

Comments of the applicant

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

☒ Yes

☐ No

☐ Not applicable – the applicant did not comment

Reasons for introducing the changes and changes made to the opinion

The applicant in his comments objects to the conditions set by RAC in its current wording, as it is technically and practically infeasible across all DUs, representing disproportionate and significant costs for EU healthcare systems and thus putting at risk the supply of critical diagnostic tests across the EU. The applicant argues that the statement in the Draft Opinions that some DUs indicated that collection and incineration is feasible to some extent does not take into account the full scenario, since it is only feasible in very specific cases and under certain prerequisites. Specifically, the applicant elaborated on: costs to comply with the conditions, impracticalities and environmental impacts of complying with conditions, fair conditions for all market participants and proactive work underway to minimise releases.
However, RAC and SEAC have already considered in their opinions the information originally provided by the applicant in their application dossier, as well as in the responses to RAC and SEAC questions where the applicant discussed the impacts in the scenario where OPE-containing wastewater was segregated and sent for incineration. This information is summarised in sections 1.2 and 5.1 of this opinion.

The opinion was slightly updated in sections 1.2 and 5.1 to take note of more detailed information provided by the applicant on costs of wastewater incineration and the wastewater transport logistics, but the overall conclusions were not changed.

The applicant furthermore commented that in early 2020 when the COVID-19 situation became a global public health emergency, the applicant began developing antigen and antibody diagnostic tests. In feasibility testing, some of the antibody tests under development were found to perform most effectively with an existing 4-tert-OPnEO -containing reagent used with several other diagnostic test kits and on analyser systems already described in its Application for Authorisation (Use 4), and which would be used by customers in the same way as is

described under this use.

The applicant reported that to design a new reagent without 4-tert-OPnEO would have added significant extra time (months, possibly years) on the time to design (please note that registration in countries which typically adds years to commercialising tests is not required in a public health emergency, with ‘emergency use’ status granted)

The applicant states that the COVID-19 antibody tests could affect the annual volumes of 4-tert-OPnEO used and forecasted in his application. At this time, however, it is not possible to confirm how those volume numbers will be affected.

While clearly the volume of this reagent could increase in line with its use in the COVID-19 test, the demand for our other diagnostic tests which use this same reagent has decreased while healthcare systems focus their diagnostic testing on COVID-19 and associated inflammatory markers. As such, in the near-and intermediate-term it is possible 4-tert-OPnEO volumes overall will not increase, may stay flat or even be at a lower level than the applicant the applicant has forecasted depending how the COVID-19 situation continues to develop.

As the need for continued COVID-19 testing evolves, this test and the component reagents will be assessed for future re-design, as described in the applicant’s Application for Authorisation for this use (Use 4).