Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated and 4-Nonylphenol, branched and linear, ethoxylated

Use 3: Use of Octyl- and Nonylphenolethoxylates in in vitro diagnostic (IVD) assays specified in Appendix 1 to the AoA.

Submitting applicant

Roche Diagnostics GmbH

ECHA/RAC/SEAC: AFA-O-0000006833-69-02/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	**Roche Diagnostics GmbH** (position in supply chain: downstream)
Substance ID EC No CAS No	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated; OPnEO 4-Nonylphenol, branched and linear, ethoxylated; NPnEO - -
Intrinsic properties referred to in Annex XIV	☐Carcinogenic (Article 57(a)) ☐Mutagenic (Article 57(b)) ☐Toxic to reproduction (Article 57(c)) ☐Persistent, bioaccumulative and toxic (Article 57(d)) ☐Very persistent and very bioaccumulative (Article 57(e)) ☒Other properties in accordance with Article 57(f) - effects to the environment
Use title	**Use 3: Use of Octyl- and Nonylphenolethoxylates in in vitro diagnostic (IVD) assays specified in Appendix 1 to the AoA**
	Other connected uses: Use 2: Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of in vitro diagnostic (IVD) assays specified in Appendix 1 to the AoA Use 4: Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of in vitro diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)
	Same uses applied for: not applicable

Use performed by	☐ Applicant ☒ Downstream User(s) of the applicant
Use ID (ECHA website)	0171-03 0171-04
Reference number	11-2120816696-45-0003 11-2120816696-45-0004
RAC Rapporteur RAC Co-rapporteur	LEINONEN Riitta MOLDOV Raili
SEAC Rapporteur SEAC Co-rapporteur	DELCOURT Benjamin SHAKRAMANYAN Nikolinka
ECHA Secretariat	GILIOLI Roberto PENNESE Daniele

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	17/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	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 11/09/2019 and 05/11/2019 Links: 0171-03: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23845/del/200/col/synonymDynamicField_302/type/asc/pre/2/view 0171-04: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23846/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: 30/03/2020, agreed by consensus.
	SEAC: 05/12/2019, agreed by consensus.
Date of sending of the draft opinion to applicant	11/05/2020
Date of decision of the applicant to comment on the draft opinion, in accordance with Article 64(5)	15/06/2020
Date of receipt of comments in accordance with Article 64(5),	17/07/2020 Note: The received applicant's comments where related to Uses 2 and 4 only.
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.

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

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

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

The proposed additional conditions for the authorisation are expected to result in the risk being limited in an appropriate and effective way.

The use applied for may result in up to approximately 524 kg of 4-tert-OPnEO and 32 kg of 4-NPnEO per year of emissions of the substances to the environment. This is equivalent to less than 52 g of 4-tert-OPnEO and less than 3 g of 4-NPnEO on average per each of the more than 10 000 of the applicant's analysers installed throughout the EEA.

THE OPINION OF SEAC

SEAC has formulated its opinion on:

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

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

The alternatives that have been assessed are listed in table 5 of the Analysis of Alternatives document in the application.

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

- By the Sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant or their downstream users.
- 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 to patients are at least €500m per year. Other impacts have been quantified, but not considered by the applicant in

the calculation of cost of non-use per kg of prevented emissions (avoided foregone profits, avoided costs for breach of contract and avoided social costs of unemployment). Other benefits have been assessed qualitatively but have not been quantified (avoided impacts on hospitals beyond the costs of claims for breach of contract).

- Risks to the environment of shortlisted alternatives have not been quantified. There may therefore be a risk arising due to the use of an alternative should the authorisation not be granted.

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

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

- cease altogether
- be taken up by market actors using the same substance (having an authorisation) operating inside the EU
- be substituted by market actors operating inside the EU
- be taken up by market actors operating outside the EU.

SEAC considered that, if an authorisation was refused, it was likely that in the European Union at least 414 jobs would be lost.

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

Additional conditions for authorisation are proposed. These are listed in section 7 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 **7-year** review period is recommended for this use.

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 ☒ downstream user
Indicative number and location of sites covered	> 10 000 analysers installed at downstream user sites across the EU
Annual tonnage of Annex XIV substance used per site (or total for all sites)	646.3 kg per annum of 4-tert-OPnEO and 54.8 kg per annum of 4-NPnEO
Functions of the Annex XIV substance.	Used in IVD assays as auxiliary chemicals in one or several liquid reagents. The specific functions vary in different IVD assays, but the typical ones are: increasing solubilisation of reagents, cell lysis, protein stabilisation and acting as a wetting agent.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	IVD assays. Product groups: 4-tert-OPnEO: Clinical chemistry, Drug monitoring, Accutrend®, Blood Gas and Electrolyte Analysis, Roche Molecular Diagnostics, Advance staining assays 4-NPnEO: Clinical chemistry, HIV Assay, Drug monitoring, Urinalysis (Test strips)
Shortlisted alternatives discussed in the application	Alternative substances considered: Some 40 shortlisted substances listed in table 5 of the Analysis of Alternatives document of the application for authorisation. Alternative technologies considered: None described Others: • Use of alternative assays (supplied by the applicant) already on the market • Replacement with new generation products developed by the applicant • Replacement of the products with assays (or reagents) from competitors Replacement of the applicant's analysers/systems with alternative analysers/systems from competitors
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
The applicant has used the PNEC recommended by RAC	☐Yes – [link to the relevant document] ☐No – [alternative values used] ☒Not relevant
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 considered	☒Yes ☐No
Adequate control demonstrated by applicant for the relevant endpoint	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of combined exposure/release used by applicant for risk characterisation	<u>Release:</u> Water: to waste water, adapted ERC8a ES-1, OPnEO: 523.5 kg/year ES-1, NPnEO: 31.8 kg/year This is equivalent to less than 52 g of 4-tert-OPnEO and less than 3 g of 4-NPnEO on average per each of the more than 10 000 of the applicant's analysers installed throughout the EEA. Wide dispersive use in laboratories/hospitals /ambulatory points of care. Air: 0 g/year (considering the low vapour pressure of the substances, emissions to air are considered negligible) Soil: 0 g/year (the substances are handled indoors, direct releases to soil are not likely)
Risk Characterisation	Environmental compartments: The applicant did not attempt to derive PNECs or RCRs. The CSR describes the OCs and RMMs in the Exposure Scenarios (ES).

Applicant is seeking authorisation for the period of time needed to finalise substitution (‘*bridging application*’)	☒Yes ☐No ☐Unclear (for some products, alternatives have been identified already, while for some feasibility testing is still going on)
Review period argued for by the applicant (length)	7 years
Most likely Non-Use scenario	Two “extreme” Non-Use Scenarios envisaged: • Competitors can take over the applicant’s market share, and all substitutions are completed as planned • Competitors cannot take over the applicant’s market share, and all substitutions are delayed until the end of the review period The applicant considers the reality will be somewhere in between these two scenarios.
Applicant conclude 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	Avoided foregone profits and avoided costs for breach of contract quantified, but not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions.
Society’s benefits of continued use	In addition to the applicant’s benefits of continued use, avoided impacts on patients of at least €500m-€5 000m per year for the years where such impacts occur. Additionally, avoided social costs of unemployment and avoided impacts on hospitals.
Monetised health impact on workers	Not applicable
Distributional impacts if authorisation is not granted	Summarised in sections 5.2 and 5.4
Job loss impacts if authorisation is not granted	At least 414 jobs would be lost in the EU

SUMMARY OF RAC AND SEAC CONCLUSIONS[1]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

RAC considers that the applicant has not demonstrated that RMMs and OCs are appropriate and effective in limiting the risk to environmental compartments.

RAC takes note of SEAC's views that the applicant's ongoing and planned substitution activities are well-described and that the plans presented by the applicant are appropriate to achieving substitution in the review period applied for, with most substitutions being achieved in the first few years. Total yearly releases are therefore expected to steeply decline already in the two years immediately after the sunset date.

RAC further notes that implementing further RMMs (collection of liquid waste for adequate treatment) would likely take a significant amount of time, which would result in most substitutions having been achieved before the additional RMMs can be implemented.

Under these specific circumstances, RAC recommends that a condition for the authorisation requiring downstream users to collect liquid wastes for adequate treatment should not be imposed in this case.

RAC takes note of the applicant's commitment to update the SDS to include current instructions for waste disposal (solid waste and reagents) or otherwise communicate them to the customers. For the authorisation RAC proposes a condition to implement the substitution activities described in the application.

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

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

2. Exposure Assessment

Releases to the environmental compartments

Air: negligible
Water: 523.5 kg/year 4-tert-OPnEO and approximately 31.8 kg/year of 4-NPnEO (release to wastewater). This is equivalent to less than 52 g of 4-tert-OPnEO and less than 3 g of 4-NPnEO on average per each of the more than 10 000 of the applicant's analysers installed throughout the EEA.
Soil: negligible

Conclusions of RAC:

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

There are uncertainties in the assessment related to the wide dispersive use and lack of detailed information on RMMs used by customers. More than 10 000 analysers have been installed in the EEA.

RAC considers the approach taken by the applicant to estimate release factors as a worst-case approach.

Does RAC propose additional conditions[2] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC recommend to the applicant monitoring arrangements[3] relevant to the potential review report?

☐Yes ☒No

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

☐Yes ☒No

3. Risk Characterisation

Environmental compartments:

The use applied for may result in up to approximately 523.5 kg per year emissions of 4-tert-OPnEO and approximately 31.8 kg per year emissions of 4-NPnEO to the environment.

The applicant has treated 4-tert-OPnEO and 4-NPnEO as non-threshold substances. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically 4-tert-OPnEO and 4-NPnEO"* adopted at RAC-43 and as concluded by RAC at its 50th meeting.

This is in line with what was decided by the Committee, based on industry submissions contained in several applications for authorisation, that the current state of knowledge of

[2] Conditions can be proposed where RCR is > 1, OCs and RMMs are not appropriate
[2] 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. appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.
[3] 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.

the endocrine disrupting properties, mode(s) of action and effects of 4-tert-OPnEO in the environment is insufficient to determine a threshold.

4. Analysis of alternatives and substitution plan[4]

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

646.3 kg per year of 4-tert-OPnEO and 54.8 kg per year of 4-NPnEO

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

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

☒Yes ☐No

Conclusions of SEAC

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

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

☐Yes ☒No

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

[4] 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*".

☐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,
- additional information provided by the applicant in response to questions from SEAC and RAC,
- RAC's assessment of the risks to the environment.

6. Proposed review period for the use

☐ 4 years

☒ 7 years

☐ 12 years

☐ Other – … years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For the environment ☒Yes ☐No

SEAC

Additional conditions: ☐Yes ☒No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For the environment ☐Yes ☒No

SEAC

Monitoring arrangements ☐Yes ☒No

9. Recommendations for the review report

RAC

For the environment ☐Yes ☒No

SEAC

AoA ☐Yes ☒No

SP ☐Yes ☒No

SEA ☐Yes ☒No

10. Applicant comments on the draft opinion

Has the applicant commented the draft opinion?

☐Yes ☒No

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

☐Yes ☒No

JUSTIFICATIONS

0. Short description of use

The use applied for covers the continued use of 4-tert-OPnEO and 4-NPnEO in in-vitro diagnostic (IVD) assays. A wide variety of IVD assays are covered by the use and the applicant specifies these in Appendix 1 to the AoA. This use takes place at the sites of the applicant's downstream users (e.g. laboratories, hospitals).

This use is related to two other uses applied for by the applicant at the same time: Use 2 (formulation and filling of the IVD assays covered in Use 3) and Use 4 (production of proteins and conjugation of latex beads, which are used as components or for the production of components of in vitro diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications). Due to this interrelation, the applicant has performed the assessment of the Analysis of Alternatives jointly for Uses 2 and 3, and the Socio-Economic Analysis jointly for Uses 2, 3 and 4 (however, some elements have been disaggregated between Uses 2 and 3 and Use 4). The applicant has also submitted a separate application for Use 1 (use of 4-tert-OPnEO as an emulsifier in the siliconisation of glass containers used for two medicinal products), but this use is unrelated to Uses 2, 3 and 4.

The tonnage is 646.3 kg per year of 4-tert-OPnEO and 54.8 kg per year of 4-NPnEO.

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

Table 1: Contributing Scenarios presented in the Use

Contributing scenario	ERC	Name of the contributing scenario
ES-1 4-tert-OPnEO	ERC8a	Use in IVD assays for laboratories/hospitals/ambulatory points of care
ES-1 4-NPnEO	ERC8a	Use in IVD assays for laboratories/hospitals/ambulatory points of care

The use covers 19 assays for several product groups and takes place at laboratories/hospitals/blood banks/ambulatory points of care in EEA countries. 4-tert-OPnEO/4-NPnEO are used for different purposes in reagents/solutions for IVD assays. 4-NPnEO is in addition used for test strips.

IVD assays with reagents containing 4-tert-OPnEO/4-NPnEO from Roche Diagnostics GmbH are used for the measurements of parameters in Clinical Chemistry (CC), Drug Monitoring (DM), HIV, Blood Gas and Electrolyte (BGE), Accutrend® (AC), Urinalysis (UA) Roche Molecular Diagnostics (RDM) and Roche Tissue Diagnostic (RTD) for diagnostic purposes in healthcare.

For CC/DM or HIV assays, laboratories and hospitals receive different types of reagents/solutions in form of small cartridges which may contain up to 3 different reagents/ solutions. These cartridges are typically inserted directly as such in the corresponding slot of the IVD instrument. From there, the different reagents / solution required for the analyses are automatically pumped and pipetted to the samples to allow the reaction to occur. Once the reaction is completed, the samples are analysed differently depending on the parameter being measured.

The Hb Calibrator used in BGE is supplied to users in hospitals in ampoules of 1.2 mL each.

Once every 90 days, one Hb Calibrator ampoule is used to calibrate the CO-Oximeter module of the cobas® b 221 system.

Similarly, RMD test tubes are inserted in the instrument with the reagents, the sample is added, and tubes are closed, removed and disposed of as waste after the measurement.

For RTD, laboratories and hospitals receive the wash buffer as a 10x pre-concentrate which is then diluted with water to a working 2x solution. The 2x solution is placed on the instrument in a carboy and is applied to applicable slides via the automated fluidics module on the instrument.

The usage is less automated for UA and AT assays, which are used mainly at ambulatory points of care: For the AT assays, ambulatory points of care and laboratories typically receive the calibration solution containing 4-tert-OPnEO in form of a 6 individual 1.5 to 2 mL dropper bottles. The control is run once per working day in applying one drop of the control solution (corresponding to 40 µL) onto a test strip inserted into the Accutrend® plus measuring instrument. Once opened, the dropper bottle can be used for up to 60 days.

In the UA assay, either automated on an instrument or manually, the test strip is dipped into a beaker filled with urine to allow the reaction to take place. Leaching of 4-NPnEO from the test strips is not taking place during the test. Manual reading may also be performed in a similar way directly by health care professionals or patients.

0.2 Key functions and properties provided by the Annex XIV substance

4-tert-OPnEO and 4-NPnEO are used in IVD kits due to their surface-active properties, and are usually used as an auxiliary chemical in one or several liquid reagents. Typical functions are: increasing solubilisation of reagents, cell lysis, protein stabilisation and acting as a wetting agent (but there are others, such as reducing carryover effect from one sample to the following, reducing matrix interferences, and decreasing assay imprecision by reducing the surface tension of the solution which leads to more precise pipetting in the instruments).

The specific function of the substance varies between the different assays covered in this use. In section 3.3 of the Analysis of Alternatives (AoA) and section 2.7.1.1 of the Socioeconomic Analysis (SEA) documents, the applicant provides detailed descriptions of the different product groups covered and the specific function of 4-tert-OPnEO or 4-NPnEO in the products that are part of those groups.

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

The products made with 4-tert-OPnEO and 4-NPnEO are IVD assays. IVD assays function based on different principles. They all have in common that a target marker in patient samples such as blood or urine shall be qualitatively or quantitatively determined. Therefore, IVD assays do not come into direct contact with patients.

The types of IVD assays covered by this use are various and can be divided into different product groups. The following description refers to the products affected within those product groups:

1. Clinical chemistry: Measurement of different blood and urine clinical parameters (e.g. creatinine in serum / plasma to monitor a patient's kidney function or the presence of C-reactive protein, which is a marker to predict the risk of coronary heart disease in apparently healthy persons and is also used to for detecting inflammatory processes related to bacterial infections).

2. Drug Monitoring Subgroups 1 and 2: Measurement of concentrations of drugs or their metabolites in urine (subgroup 1) and serum / plasma (subgroup 2) samples with the goal of detecting abuse of drugs or monitoring therapies performed with these drugs.
3. HIV: Screening test to determine the presence of HIV antigens and antibodies in blood or plasma samples for early detection of HIV infection.
4. Blood Gas and Electrolyte Analysis: Measuring of several parameters in whole blood, serum, plasma, pleural fluid, aqueous solutions, acetate, bicarbonate and dialysis solutions (e.g. O_2, CO_2, pH, Glucose, Lactate, Urea, Sodium, Potassium, Bilirubin, Haemoglobin, etc.). Used in situations where fast and accurate results needed (e.g. ICUs, ERs, operating rooms, neonatal stations).
5. Accutrend®: This is a handheld device used in physician's practices and clinics for the determination of metabolic disorders and cardiovascular risk factors. The affected product in this portfolio is a control solution for checking the performance of the test strips for whole cholesterol measurement in blood.
6. Urinalysis: Urine multiple test strips are used to measure certain constituents in urine which are indicative of renal, urinary, hepatic and metabolic disorders.
7. Roche Molecular Diagnostics:
    - Subgroup RMD1: Test used to detect Flu A and B in nasopharyngeal swabs.
    - Subgroup RMD2: MRSA Test for the direct detection of methicillin-resistant Staphylococcus aureus from nasal swabs and its antibiotic susceptibility profile.
8. Roche Tissue Diagnostics: Tissue samples are evaluated by selective staining with in situ hybridisation (ISH) probes to aid in the diagnostic of different types of cancer (e.g. cervical cancer, breast cancer).

These products are used across the healthcare market sector by hospitals and laboratories mainly, but also by blood banks and researchers.

0.4 Downstream User survey

The applicant collected information on the liquid waste management of their downstream users in the 9 countries with the largest number of the applicant's instruments installed (France, Germany, Italy, Sweden, Austria, Spain, Belgium, Poland and Greece). The information gathered through their country affiliates covered:

- General information on national legislation and handling of liquid waste in the country
- Information on one to two example laboratories for each country, including waste volumes

Additionally, further information was requested from a few selected countries where no collection and treatment of laboratory wastewater is conducted (Sweden, Germany, Austria, and Belgium).

Data was received from most, but not all, of the countries. Details on example laboratories were received for 6 countries.

1. Operational Conditions and Risk Management Measures

1.1 Environment

A summary of the OCs and RMMs in the environmental contributing scenarios is provided below. The detailed conditions of use are available from sections 9.4 and 9.5 of the CSR.

Operational conditions

Volumes

- 4-tert-OPnEO: 646.3 kg/year
- 4-NPnEO: 54.8 kg/year
  Number of days of release per year: 365
- Daily release
  - ES-1: 3.28×10^{-4} kg/day 4-tert-OPnEO (1.12×10^{-4} kg/day $OP_{equiv.}$)
  - ES-1: 2.1×10^{-5} kg/day 4-NPnEO. (6.99×10^{-6} kg/day $NP_{equiv.}$)

The operational conditions and risk management measures with respect to waste vary from one IVD module to the other and between different IVD assays. Risk management measures also vary significantly from one laboratory/hospital to the other and between countries.

There are two types of waste fractions: waste from unused product and waste from the instruments after the assays have been performed.

Once used, empty reagent cartridges may still contain a dead volume of unused reagent which cannot be removed from the flasks. All unused reagents in cartridges (e.g. from CC or DM assays) and flasks (e.g. containing the AT control solution) will be disposed of as if they were hazardous solid waste despite most of these reagents are not classified as hazardous waste according to the waste regulations. At the time of preparation of this dossier, handling of waste from cartridges was not yet managed in a harmonized way across the applicant's EEA customers. This will be achieved by changes in the SDS and, if necessary, additional/ separate communication to customers.

Waste from the instruments after assays have been performed is disposed of as hazardous solid waste in the following cases:

- Some assays, where the reagents remain in a closed tube, are disposed of afterwards
- For some instruments, cuvettes that have been used still contain the reagents and are disposed of as such
- Test strips that contain the 4-tert-OPnEO/4-NPnEO themselves (e.g. UA) or contain a control solution with 4-tert-OPnEO

However, for most instruments on which CC/DM or HIV assays are run, 4-tert-OPnEO and 4-NPnEO are contained in concentrated liquid reagent waste from the instruments (high-concentrated waste). This waste is either collected in a container or mixed with the diluted waste from rinsing steps (low-concentrated waste) and then directly released to wastewater. The low-concentrated waste is estimated to contain less than 1 % of the reagent volume and therefore, less than 1 % of the overall amount of 4-tert-OPnEO/4-NPnEO used. Disposal of the concentrated waste depends on the applying local regulations on liquid waste as well as the setup of the laboratories. In some countries, treatment of waste for biohazard is required. Treating (infectious) waste for biohazard means the inactivation of possibly infectious germs (i.e. pathogens), e.g. by heating under pressure (autoclaving), incineration or chemical treatment.

Most releases to wastewater occur from CC/DM and HIV assays which run on different cobas® instruments. The only other product group from which release to wastewater occurs is RTD. The substitution project to replace 4-tert-OPnEO in the wash buffer used for RTD assays is planned to be completed by 28/02/2020 including a change in production. It is currently estimated that with a likelihood of ca. 95 % the substitution will be completed on time. It is expected that by the sunset date only few stocks would remain at customers' sites in EEA and emissions would be eliminated soon afterwards, but at the latest by 28/02/2022 due to shelf life. Therefore, details on operational conditions and RMMs for RTD are not available in the CSR.

The estimated concentrations in liquid waste from CC/DM or HIV modules range from 0.1-50 mg/L 4-tert-OPnEO or 4-NPnEO in high concentrated liquid waste, from 0.0001-0.1 mg/L in low concentrated liquid waste and from 0.01-10 mg/L in combined liquid waste. The actual 4-tert-OPnEO/4-NPnEO concentration at any given time also depends on the working regime of the instrument.

The total waste volume generated by the instruments in 2021 from CC/DM in EEA is estimated to be 12 000-78 000 m^3 (high concentrated waste), 160 000-765 000 m^3 (low concentrated waste) and 172 000-843 000 m^3 (combined, high and low concentrated waste). The corresponding volumes for HIV are 7 000-32 000 m^3, 97 000-408 000 m^3, 104 000-441 000 m^3, respectively.

Table 2: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	None (substance not volatile).	No emission to air is expected due low vapour pressure of the substance and indoor use in assays.
Water	Collection in the container. Diluted and released to wastewater. Treated as biohazard waste.	Depending on assay. See above. Treatment in municipal STP.
Soil	None (no direct release to soil)	No direct release to soil at site
Waste	Solid waste treated as hazardous waste (SDS and communication to customers)	Depending on the assay, country, type of waste. See above.

Substitution activities

The applicant explained that as a result of their planned substitution activities, at the downstream sites the total annual tonnage of 4-tert-OPnEO should decrease from 529 kg/a at the sunset date to reach almost 0 in 2024 if the substitutions are completed in time in the formulated reagents. This is in line with the delay due to the shelf life of the products. The applicant also describes the impacts of a worst-case scenario, which would happen if all the different substitution projects encountered such difficulties that all substitutions are delayed to the end of the review period. This would mean a maximum annual usage of 646.3 kg/a from all uses at the downstream sites until the end of the review period.

At the downstream sites, the total annual tonnage of 4-NPnEO should decrease from 52.8 kg/a in 2020 to 27 kg/a at the sunset date, decreasing gradually until the end of 2027, if the substitutions are completed in time in the formulated reagents. This is in-line with the delay

due to the shelf life of the products. If all substitution projects failed and all the substitutions are delayed to the end of the review period, a total annual usage of 53.3 kg/a from all uses at the downstream sites could potentially be reached at the sunset date as a worst-case.

See Section 4 and Annex I for more information on the applicant's planned substitution activities.

1.2 Discussion on OCs and RMMs and relevant shortcomings or uncertainties

All solid waste is recommended by the applicant to be treated as hazardous waste, even if all solid waste is not classified as hazardous waste by the waste legislation. Instructions on waste treatment are given in the SDS and in communication to customers. Disposal of the liquid waste depends on the applying local regulations on liquid waste as well as the setup of the laboratories. Liquid waste is released to wastewater from CC/DM, HIV, and RTD assays, specifically.

Depending on the instrument, waste handling as recommended in the operator manuals or SDS is different. The current instructions for disposal of reagents in the SDS will be updated. The foreseen updated text for each product group is given in Table 10 of the CSR. The instructions concerning liquid waste refer e.g. to local regulations, to relevant water discharge facility regulations, to treatment as infectious waste and to relevant laws and local regulations. The applicant does not intend to include instructions for incineration of 4-tert-OPnEO/4-NPnEO-containing liquid waste in the instructions.

The applicant is of the opinion that further reduction of the release of 4-tert-OPnEO/4-NPnEO to wastewater is not practically feasible. Separate collection of concentrated liquid waste in countries where this is not common practice is not considered feasible to be implemented within a reasonable timeframe and at reasonable cost. On the one hand, the applicant states that suitable methods other than incineration to eliminate 4-tert-OPnEO/4-NPnEO at the low concentrations present in liquid waste are not available. Incineration would require large amounts of energy and thus lead to high CO_2 emissions and high cost. Furthermore, adaptation of laboratory installations to collect or treat the large amounts of wastewater would be a major logistical challenge and require reconstruction or modification of buildings in many cases. Therefore, the implementation of any kind of waste disposal/treatment, if possible, in all laboratories would take considerable time. Consequently, these measures would only become effective at a time when the majority of emissions is expected to be already eliminated due to completed substitutions.

Another possible alternative, the redevelopment and installation of instruments to selectively collect or treat 4-tert-OPnEO/4-NPnEO-containing waste would take longer than the completion of all substitutions by the end of the review period.

Therefore, according to the applicant substitution of 4-tert-OPnEO and 4-NPnEO in the reagents as fast as possible is considered the only option to further reduce the emissions and to eliminate them latest by the end of the review period.

1.3 Conclusions on OCs and RMMs

RAC considers that the applicant has **not** demonstrated that the OCs and RMMs are appropriate and effective in limiting the risk to environmental compartments.

RAC takes note of SEAC's views that the applicant's ongoing and planned substitution activities are well-described and that the plans presented by the applicant are appropriate to achieving

substitution in the review period applied for, with most substitutions being achieved in the first few years. Total yearly releases are therefore expected to steeply decline already in the two years immediately after the sunset date.

RAC further notes that implementing further RMMs (collection of liquid waste for adequate treatment) would likely take a significant amount of time, which would result in most substitutions having been achieved before the additional RMMs can be implemented.

Under these specific circumstances, RAC recommends that a condition for the authorisation requiring downstream users to collect liquid wastes for adequate treatment should not be imposed in this case.

RAC takes note of the applicant's commitment to update the SDS to include current instructions for waste disposal (solid waste and reagents) or otherwise communicate them to the customers. For authorisation RAC proposes a condition to implement the substitution activities described in the application.

Overall conclusion

Are the operational conditions and risk management measures appropriate[5] and effective[6] 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

2. Exposure assessment

2.1. Environmental emissions

Air

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

Soil

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

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

Table 3 Summary of environmental emissions of 4-tert-OPnEO and 4-NPnEO

Release route	Release factor	Release per year to waste water (*	Release estimation method and details
Water	ES-1: OPnEO: 81 % ES-1: NPnEO: 58 % ERC 8a release factor excluding the waste percentage	523.5 kg 31.8 kg	Depending on the assay and the instrument, unused product as well as parts of used assays/ reagents are collected and disposed of as waste. The rest is going to waste water.
Air	0		The use of reagents containing 4-tert-OPnEO or 4-NPnEO is in a closed analyser, emissions to air are considered negligible.
Soil	0		4-tert-OPnEO and 4-NPnEO are handled indoors. Direct releases to soil are not possible.

(* based on the maximum total amount multiplied by the average release factor

Water

4-tert-OPnEO/4-NPnEO are used for different purposes in reagents/solutions/test strips for IVD assays. Therefore, the relevant environmental release category is ERC 8a - Wide-dispersive indoor use of processing aids in open systems (Indoor use of processing aids by the public at large or professional use). The default environmental release factors for ERC 8a are 100 % release to water before STP. However, with substance and use-specific information, the assessment factor was refined by assessing the waste from different IVD assays and instruments. An overall fraction going to waste was derived taking into account the RMMs. The default release factor to wastewater of 100 % as foreseen for ERC 8a was adapted by subtracting the fraction going to waste (19 % for 4-tert-OPnEO, 42 % for 4-NPnEO), leading to a final release factor of 81 % of total 4-tert-OPnEO and 58 % of total 4-NPnEO, respectively.

The estimated releases are 523.5 kg/year 4-tert-OPnEO and 31.8 kg/year 4-NPnEO, based on the maximum total amount multiplied by the average release factor.

The applicant had collected information on specific laboratories for EEA countries. Depending on instrument, assay, country and laboratory, 4-tert-OPnEO- and 4-NPnEO-containing liquid waste is being collected and treated (treated with a pre-treatment module or chemical treatment) or directly released to wastewater. Treatment is mainly targeted towards biohazard rather than removal of specific chemicals. Due to the large variations as discussed above and the uncertainty regarding the efficiency of treatment methods towards 4-tert-OPnEO and 4-NPnEO removal, it is not possible to estimate actual removal of these compounds.

According to the applicant, if the substitutions are completed as planned in the formulated reagents, the total release of 4-tert-OPnEO to wastewater at the downstream sites should decrease from 426.8 kg/a at the sunset date to reach 0 in 2024, in line with the delay due to the shelf life of the products. The applicant also describes the impacts of a worst-case scenario, which would happen if all the different substitution projects encountered such difficulties that all substitutions are delayed to the end of the review period. This would mean a maximum total annual release of 522.2 kg/a to wastewater from all wide-dispersive uses until the end of the review period (Note: this figure which is given in the CSR is equivalent to the 523.5 kg/year

4-tert-OPnEO stated above. The slight difference is due to applying individual release factors per product group versus applying an average release factor to the total amount and resulting differences from rounding).

The total release of 4-NPnEO to wastewater at the downstream sites should decrease from 10.8 kg/a at the sunset date to reach 0 at the end of the review period in line with the delay due to the shelf life of the products if the substitutions are completed in time. If all substitutions are delayed to the end of the review period for all formulation activities, a maximum total annual release of 31.8 kg/a to wastewater from all wide-dispersive uses could potentially be reached as a worst-case in 2023.

See Section 4 and Annex I for more information on the applicant's planned substitution activities.

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

There are substantial releases to wastewater from the liquid waste related to the use of IVD assays in laboratories/hospitals/blood banks/ambulatory points of care. Efficacy of possible onsite treatment of liquid waste at laboratories / hospitals cannot be estimated. Hence it was assumed that any onsite treatment of wastewater would not reduce 4-tert-OPnEO/4-NPnEO in wastewater. The approach can be considered as worst-case.

The wastewater from the use goes to municipal STPs, which is not considered as an RMM, and thus RAC does not consider the releases after the STP in the release calculation. RAC calculated the releases based on the adapted release factors for both substances.

RAC concludes that direct releases to air and soil are expected to be negligible.

2.3. Conclusions on exposure assessment

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

There are uncertainties in the assessment related to the wide dispersive use and lack of detailed information on RMMs used by customers. More than 10 000 instruments have been installed in the EEA. RAC considers that the approach taken by the applicant to estimate release factors is based on the worst-case approach.

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

3. Risk characterisation

3.1. Environment

The human health assessment (Man via environment, workers and consumers) is not considered according to: (EC) No 1907/2006 (REACH).

The applicant has treated 4-tert-OPnEO and 4-NPnEO as non-threshold substances. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically 4-tert-OPnEO and 4-NPnEO"* adopted at RAC-43 as concluded by RAC at its 50th meeting.

Based on the OCs & RMMs RAC is of the view that the applicant has not demonstrated that releases to environmental compartments have been prevented or minimized as far as technically and practically possible (with the view of minimizing the likelihood of adverse effects).

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

The applicant compared the predicted environmental concentrations (PECs) with predicted no-effect concentrations (PNECs) for freshwater/marine aquatic/sediment organisms and soil or Environmental Quality Standards (EQS) for 4-tert-OP and 4-tert-NP of the Water Framework Directive (Directive 2000/60/EC). 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 and 4-NPnEO.

Furthermore, at RAC 50, the 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.

The use applied for may result in up to approximately 524 kg of 4-tert-OPnEO and 32 kg of 4-NPnEO per year of emissions of the substances to the environment. This is equivalent to less than 52g of 4-tert-OPnEO and less than 3 g of 4-NPnEO on average per each of the more than 10 000 of the applicant's analysers installed throughout the EEA.

4. Analysis of Alternatives and substitution plan[7]

Several options for removing 4-tert-OPnEO/4-NPnEO from affected products have been considered by Roche.

1- Substitution with alternative surfactants in the existing IVD assays.
2- Use of alternative assays (supplied by the applicant) already on the market
3- Replacement with new generation products developed by the applicant
4- Replacement of the products with assays (or reagents) from competitors

Option 1 is considered as the most realistic for most products, and therefore the applicant is focusing research efforts on it.

Regarding the replacement of the applicant's analysers/systems with alternative analysers/systems from competitors, although no formal analysis is presented in the Analysis of Alternatives, there is information in the Socio-Economic Analysis. One of the scenarios the applicant assessed assumes that competitors are able to take over the applicant's market share.

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

646.3 kg per year of 4-tert-OPnEO and 54.8 kg per year of 4-NPnEO.

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

As mentioned above, several options for the replacement of the 4-tert-OPnEO/4-NPnEO-containing products have been considered by Roche.

Option 1, substitution with alternative surfactants in the existing IVD assays, is considered as the most realistic for most products. The applicant has experience with already completed substitution and the development of new products has shown that, in principle, substitution of 4-tert-OPnEO and 4-NPnEO is possible.

Option 2 consists of the replacement of the assays by other existing assays (supplied by the applicant) free of the substance applied for. This is not possible since usually a single assay is available for each system/analyser.

Option 3 is the replacement of current products with new-generation products developed by the applicant, i.e. new formulations. This was rejected in most cases, as the applicant states

[7] 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*".

that development of new generation products takes a long time, as they must be registered as new IVDs with health authorities. Also, these new products run on new instruments and customers have to be switched to the new instruments to be able to use the new assays. The exception is the HIV assay, for which a process is already in place to introduce a new generation system, where the HIV assay is 4-NPnEO-free. The applicant explains that, due to the ongoing process to obtain market authorisation for the new system and limitations in the applicability (currently only a high-throughput instrument is available), the older systems would need to remain on the market another 10 years before the availability of the new-generation product.

Option 4 is the replacement of the affected assays with assays from competitors. This was not evaluated as a suitable alternative strategy, since the applicant's systems only run with their own assays. Moreover, there is no certainty on the agreement of competitors to sell their product at an affordable price, and no guarantee that their products are 4-tert-OPnEO and 4-NPnEO-free if they are produced outside the EU.

The applicant is therefore focusing research efforts on substituting 4-tert-OPnEO and 4-NPnEO in almost all of their products, since it's considered the most realistic option. In addition to the HIV assay, there is a second exception: a product in the Blood Gas and Electrolyte Analysis product group, which is used in a system planned to be removed from the EU market already (exact date claimed confidential, but the applicant explains that it is unlikely that substitution of 4-tert-OPnEO in the assay could be achieved before this date). This product needs to be supplied till that date due to contractual obligations.

The applicant's efforts to identify possible alternatives surfactants began already in 2015. Since the substitution is IVD-dependent, key criteria applied to identify a possible alternative depend on the group of assays and the specific function of 4-tert-OPnEO and/or 4-NPnEO in them. The applicant provides a detailed description of the function of the substances in each of the different assays.

To identify alternative surfactants, the applicant defined a list based on the basic chemical properties of the surfactants. Moreover, availability, economic feasibility and past experiences were considered. Finally, a hazard assessment of the alternative surfactants was performed to avoid regrettable substitution.

Shortlist of possible alternatives surfactants

The applicant has shortlisted a list of 41 alternative surfactants for replacement of 4-tert-OPnEO / 4-NPnEO. These alternatives are listed in table 5 in the Analysis of Alternatives document in the application.

Each of the shortlisted alternatives are relevant to different products, and are at various stages of testing: some are still undergoing feasibility tests, some are under validation, and some are already identified as the alternative that will be used. Detailed results of the testing are presented in the application. However, the applicant claims confidential the identity of the alternatives when presenting the results of the testing, and they are referred to only by number at that stage.

No comments were received during the public consultation.

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.

SEAC notes that, as described in the previous section, the applicant intends to avoid regrettable substitution and in order to do so, has performed a hazard assessment of the alternatives under consideration. The following were checked for before the potential alternatives were accepted as viable:

- No regulatory alerts.
- No aromatic rings or halogens.
- No suspected SVHCs.
- No classification as acute or chronic toxicity to aquatic organisms.
- No classification as human health hazard Cat. 1 except H318.

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

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

☐Yes ☒No

Technical feasibility

To achieve substitution, several steps need to be accomplished by the applicant, with a focus on the performance of the IVD. They have listed 4 major steps:

1. Feasibility assessment
2. Verification/validation of the assays
3. If necessary, request for regulatory approval/updated market authorisation
4. Introduction to the market

Surfactants are assessed in a complete setup (in a commercial configuration). The applicant will produce first laboratory lots of reagent/assays with the alternative surfactant being assessed. Performance testing of the IVD assays is then undertaken to test the most critical assay specifications, shelf-life and on-board stability. The process is then validated by manufacturing pilot lots and testing them.

Regarding step 3, since a specific market authorisation by the health authorities is required for IVD assays, altering an ingredient in the product has an impact on the timelines for

substitution. This can lead to three kinds of changes, with very different timings.

- Silent or minor change: *no re-approval of the IVD market authorisation by authorities is needed, as the process change does not impact information requirements of that market authorisation (silent change) or the impact on information requirements are minor and can be notified by a simplified procedure*
- Major Change: *changes to the IVD product and thus the IVD-regulatory documentation are significant and have to be communicated to authorities as a major change. The change is subject to detailed review by authorities*
- Re-registration (same product number) or new product registration: *changes to the IVD product are so important that the product is regarded as a new product. A complete dossier for a new market authorisation has to be prepared*

For each of the products, the applicant has assessed which of the three above options will likely apply, although they stress this is not certain, and the same change may trigger different authorisation requirements by health authorities in different countries.

Regarding the status of R&D, the applicant presents very detailed information about the R&D status of each product. There are some products for which substitution is already expected to be completed before the sunset date, while others are at different stages.

The applicant highlights that delays can occur at any time if technical difficulties are encountered, and several examples of when this has already happened are presented.

For each product, the applicant also provides timelines for each of the stages expected before substitution can be implemented, showing that there would be no technically feasible alternatives by the sunset date for any of the affected products.

Economic feasibility

The applicant has provided an estimate of the investment costs that are foreseen for the different groups of IVD (the amounts presented in the application are claimed confidential). The applicant stresses that the main cost driver are the additional regulatory requirements in case of a re-registration being needed. These requirements are translated into additional experiments that need to be performed to provide the requested data.

The applicant states that they consider substitution to be economically feasible. They explain that they have a company-wide public commitment to substitute any SVHC used in their products or processes, where technically possible, within 10 years of their inclusion on the EU Candidate List.

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

SEAC considers that the analysis of alternatives is sufficiently detailed to conclude on the technical and economic feasibility of the alternatives.

The applicant describes the use applied for in detail and the requirements associated with each IVD product. The applicant has covered in detail the feasibility and validation studies required, as well as the impact substitution would have on the market authorisation. The applicant has also clearly described current R&D results on the possible alternatives, including the timeline for possible substitution. Alternatives have already been implemented for several products, which are therefore out of the scope.

The applicant has presented a shortlist of 41 possible alternatives and the current status of

the R&D associated with each product. The steps necessary to achieve substitution are presented and clearly detailed. The limitations faced by the applicant are clearly described and enable SEAC to draw its opinion on them.

Based on the applicant's assessment concerning potential alternatives in the different product groups, and the necessity to achieve the same level of performance, SEAC considers it clear that no alternative will be available by the Sunset Date.

The clear separation between the product groups, full details on the steps needed to achieve substitution and the R&D status enable SEAC to evaluate the progress of substitution and the effort already made by the applicant. Since each of the products have clear, well-described steps to achieve substitution and clear timelines associated with them, SEAC can concur with the applicant on the review period of 7 years that is necessary to achieve substitution in all products.

SEAC also notes that no additional information regarding alternatives was received during the Public Consultation.

4.4. Substitution activities / plan

Has the applicant submitted a substitution plan?

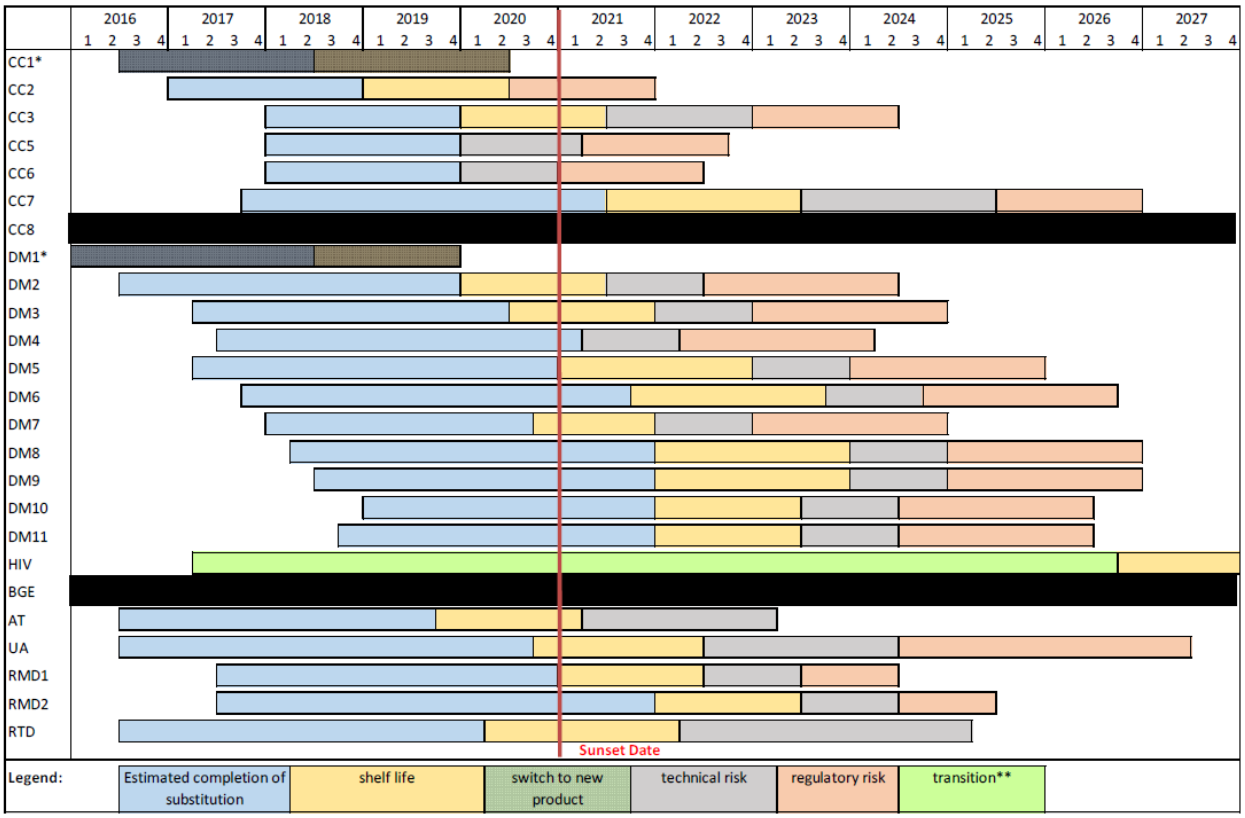
☒Yes ☐No

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

☒Yes ☐No

As presented in section 4.3, the applicant is already engaged in an R&D programme for the different IVDs in scope of the use applied for. The applicant has detailed the R&D programme for each of the different products, and provides the timelines associated with these planned activities. The applicant has a clear view on the steps needed to demonstrate the technical feasibility and achieve substitution. Some of the IVDs will be 4-tert-OPnEO/4-NPnEO-free before the sunset date and are therefore out of scope. For the others, the steps needed to accomplish substitution of 4-tert-OPnEO and 4-NPnEO are detailed in Figure 1.

Figure 1 : Replacement timeline



* Product not in the scope of this AfA

** Transition due to existing contracts and/or replacement of complete IVD systems

In addition to the activities needed to ensure substitution is technically feasible, the timeline includes:

- Time to account for technical risk, in case technical issues are encountered (as mentioned, the applicant includes examples of cases where this has happened in the past).
- Time to comply with the likely regulatory requirements associated with the change.
- A period covering the shelf life of the products, during which downstream users would continue to use products made before substitution, purchased before the new ones became available.

It should be noted that for the products where a different option than replacing the surfactants has been taken, the timelines are different. For HIV, the timeline includes only a transition to the new system, plus the product shelf-life, while for the Blood Gas and Electrolyte product the exact timing of the steps is claimed confidential.

The applicant foresees a timeline of 7 years for the complete substitution of the SVHC in all products affected, with substitution in several products expected to be achieved significantly before that time.

The applicant has provided a substitution plan. For the sections relating to 'Factors affecting substitution' and 'List of actions and timetable with milestones', the applicant for the most part refers to the AoA document in the application, which already contains detailed information on those topics. Additional information is presented in the section relating to 'Monitoring of the implementation of the substitution plan', where the applicant describes the organisational structure and provides details regarding communication between the different areas that are part of the structure overseeing the projects, and how progress of the substitution plans is followed and decisions are made if deviations occur from the timelines.

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

SEAC considers that the analysis of alternatives is sufficiently detailed to conclude on derived review period requested by the applicant.

The substitution plan, as well as the detailed description of the actions taken and planned by the applicant in the application for authorisation are sufficient to enable SEAC to conclude on the substitution activities and plan without major uncertainties. The state of progress for each product and the steps needed to be accomplished are detailed and clear. The plans presented by the applicant seem appropriate to achieving substitution in the review period applied for. The applicant is clearly committed to substituting the use of 4-tert-OPnEO/4-NPnEO in each of the products affected, either by using another solvent of by substituting them with 4-tert-OPnEO/4-NPnEO-free products. The timeline associated with substitution is plausible and acceptable to SEAC.

A review period of 7 years is needed to achieve the necessary steps to complete substitution according to the applicant. SEAC concurs with this review period needed to achieve substitution and fulfil the necessary market authorisation needed after the change of formulation.

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

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

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

5. Benefits and risks of continued use

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

☒ Yes

☐ No

5.1. Human health and environmental impacts of continued use

The applicant presents quantified estimates of releases of 4-tert-OPnEO and 4-NPnEO over time, taking into account expected sales development, planned substitution, and risk management measures.

They provide best-case and worst-case scenarios for maximum annual releases. In the best-case scenario, all the substitutions are implemented as planned. In the worst-case scenario,

all substitutions are delayed until the end of the review period.

Using that methodology, the applicant estimates that Use 3 would result in maximum annual releases of 524 kg of 4-tert-OPnEO and 32 kg of 4-NPnEO.

These amounts are released by hospitals, laboratories, blood banks, and ambulatory points of care such as physicians' practices or emergency rooms; all are downstream users of the applicant's products. The applicant does not report the number of its downstream users, but they do report the exact number of their instruments installed (larger downstream users may have several installed), which provides a good indication. The exact number is claimed confidential, but the applicant provides a non-confidential estimate of >10 000. The applicant also provides information regarding in which countries the instruments are located, but this information is claimed confidential.

The applicant also describes that downstream releases are generally well-spread over the year, and spread throughout the EEA. The applicant considers that the overall releases from their downstream uses to the environment are not expected to cause issues in the receiving environmental compartments.

Operational conditions and RMMs at the downstream users' sites are described in Section 1 of this opinion. The applicant also provides a discussion of potential additional RMMs to deal with releases to wastewater via liquid waste streams from the IVD modules, which may be directly connected to the sewer system.

One potential approach is the adaptation of modules to selectively collect waste containing 4-tert-OPnEO and/or 4-NPnEO. The applicant explains that this would require an adaptation of the modules. They consider that doing so would represent a very high cost and take enough time that substitutions of 4-tert-OPnEO and 4-NPnEO are be expected to be completed before the new modules would be available. They provide a more detailed description for the cobas® instruments, where an estimated cost is provided (although claimed confidential) and the steps required are described, showing an effort that would be comparable with developing and introducing a new analyser generation.

Another potential approach is the collection of all liquid waste from the instruments. The applicant acknowledges that this is already done in some countries (such as Italy), but states that where this is not required, space for liquid waste containers and facilities for collection by waste management companies are not foreseen during installation of laboratories. The applicant details two possible ways of doing this.

The first is by directly connecting instrument outlets for liquid waste to a larger waste container. The applicant identifies that availability of space for such a larger waste container would be a problem in many cases, and they provide some supporting information regarding the way laboratories are often highly optimised for space. In conclusion, they consider that in many cases, modifications of the laboratory building would typically be needed. This could result in high costs as well as a long time needed for implementation of the risk management measure. Costs are not estimated, but SEAC considers that given the very high number of instruments and downstream users concerned, these could be very high. Additionally, structural modifications could take a significant amount of time.

The second is by using containers for concentrated waste that are integrated onto the instruments and then emptied manually. These containers are relatively small for ergonomic reasons, and the volume of waste means that emptying could be required up to once an hour, with what the applicant considers are unacceptably disruptive effects to the operation of the laboratories. This wastewater would have to be stored in some sort of collection facility, which the applicant considers would give rise to the same considerations regarding space as directly

connecting the instruments to a larger waste container.

As a result, the applicant concludes that implementation of further risk management measures at downstream users' sites to reduce releases to the environment via liquid waste streams is not considered technically and practically feasible.

The applicant also analyses the implications of incineration if wastewater were collected. They use cobas® 6000 / 8000 and Benchmark® modules as examples, where the liquid waste generated would lead to incineration costs of €22-126m (based on costs in Germany, which are acknowledged to be higher than in other countries). Additionally, the applicant identifies other impacts, such as having to transport the waste for sometimes long distances, and the energy required for incineration, which leads to CO_2 emissions.

In response to a question from RAC and SEAC regarding potential additional RMMs, the applicant stated they would have "extremely serious concerns" if further conditions to reduce emissions were recommended. They express that such a move would disrupt the operation of their customers' business to such an extent that the healthcare services could be gravely disrupted.

SEAC considers that the information provided is enough to concur with the applicant's conclusion that implementing further RMMs would likely lead to costs of the magnitude estimated by the applicant, disruption of operation at the downstream users' sites, and in some cases take a significant amount of time, which may result in substitution having been achieved before the additional RMMs can be implemented.

5.2. Benefits of continued use

Non-use scenario

In case of refusal of an authorisation for the use applied for, the following non-use scenarios were considered and rejected by the applicant:

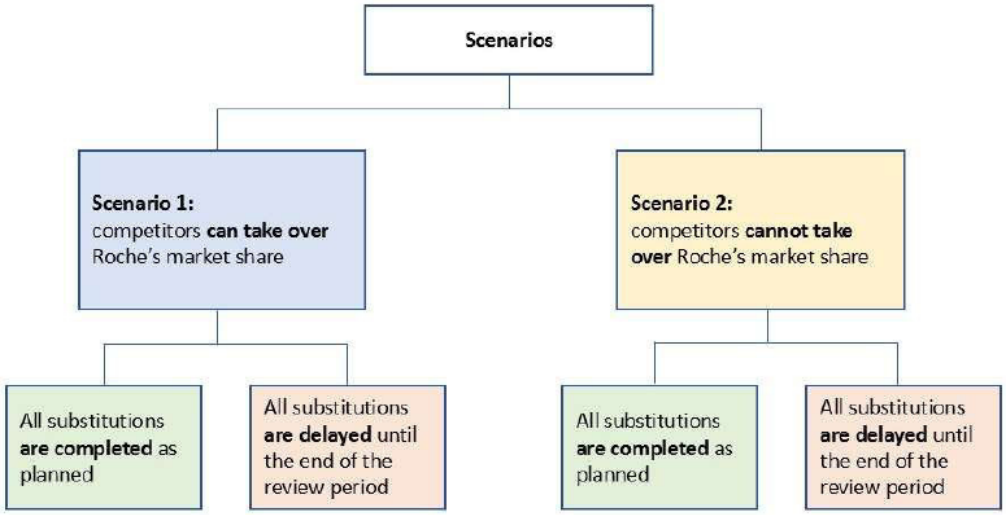
- Stock-building: Not relevant for this use.
- Relocation of production outside of EEA: Not relevant for this use.
- Replacement by materials/products from third parties to be used in the applicant's instruments: not feasible for reasons of compatibility (competitors' products are not suitable for the applicant's closed systems without modifications, which the applicant estimates would take some 3-4 years to do. Also, availability of 4-tert-OPnEO- and 4-NPnEO -free substitutes is uncertain. The capacity of competitors given the applicant's large market share may also be a problem, leading to possible price increases. This NUS would also require market authorisation.

The most likely NUS is an interruption of supply of the applicant's products until substitution is completed as described in section 4. As a result, they explain that customers would either switch to a competitor's system, if one were available, or wait until the applicant has completed substitution and is able to supply the products again (with consequent implications for patients' wellbeing).

The applicant cannot estimate in what proportion of cases alternative systems would be available. Therefore, to assess the impacts of the NUS, the applicant describes two non-use sub-scenarios which describe the extremes of what could happen regarding competitors being able to take over the applicant's systems. Under NUS1, competitors can take over the applicant's market share in all cases. Under NUS2, competitors cannot take over any of the applicant's market share (e.g. because alternative systems are not available, or because competitors' systems are also affected by non-authorisation). The applicant expects that reality will be somewhere in between: some competitor systems that are not affected will be available to replace a part of the applicant's systems.

Additionally, these two NUS can be combined with extreme scenarios regarding the success of substitution in the applicant's products: whether all are completed as planned, or whether all are delayed until the end of the review period. The figure below illustrates this:

Figure 2: Scenarios considered by the applicant



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

Depending on the availability of systems from competitors that could take over the applicant's market share, for different products, all the options below may be possible:

- the use would cease altogether
- the use would be taken up by market actors using the same substance (having an authorisation) operating inside the EU
- the use would be substituted by market actors operating inside the EU
- the use would be taken up by market actors operating outside the EU

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

At least 414 jobs would be lost.

Economic impacts of continued use

The applicant notes that the assays affected by non-authorisation are part of systems that include many other assays that do not contain 4-tert-OPnEO and/or 4-NPnEO. The lack of the affected assays would create gaps in the applicant's systems that, as explained earlier, cannot be filled by individual components from competitors. Instead, to fill the gaps customers would have to switch to a whole other system provided by a competitor, which is a process that can take up to 2 years, depending on the system (the applicant provides detailed estimates for each type of product and uses these in the calculations). This assumption affects several of the impacts calculated by the applicant.

The following impacts would be avoided under the Applied for Use scenario:

Foregone profits to the applicant

The applicant considers 3 categories of profits that would be foregone under the NUS:

- **Only affected assays** – the profits that would have been generated by the sales of the assays that contain 4-tert-OPnEO and/or 4-NPnEO. This would occur under both NUS1 and NUS2.
- **Impacted portfolio or system** – the profits that would have been generated by the sales of non-affected assays in the same portfolio or system as the affected assays, once customers have switched to a competitor's system. This would occur only under NUS1.
- **Growth of impacted portfolio or system** – the profits that would have been gained from new customers, who will not purchase the applicant's systems with gaps if other options are available. This would occur both under NUS1 and NUS2 (but would be smaller in NUS2, as it is relevant only for some systems, which would be rendered unusable by the lack of the affected assays).

For each scenario, minimum and maximum sales and profits losses are calculated, shown in the following ranges:

- Minimum losses express the situation if substitutions are completed as planned
- Maximum losses express the situation if substitutions are delayed till end of the review period

The applicant describes in detail the assumptions made in their calculations for the different product groups. On request of SEAC, the applicant provided a non-confidential range of profits expected to be foregone under each of the Non-Use Scenarios. Because of their interlinkage, these ranges were calculated for Uses 2 and 3 combined:

- If competitors can take over the applicant's market share fully (NUS1), foregone profits are estimated at €550 million to €5.5 billion
- If competitors are unable to take over the applicant's market share (NUS2), foregone profits are estimated at €50.5 million to €550 million.

These are all present values over the requested review period. Over 90 % of the expected profits foregone are reported to arise from not being able to supply existing customers (affected assays + impacted portfolio/system).

The applicant acknowledges that, under NUS1, some of their foregone profits would be opportunity gains to competitors (once customers have switched to the competitors' systems) and would hence represent a distributional impact. They note, however, that some of those competitors may be based outside of the EU and this might thus still be a welfare loss from an EU perspective.

Costs for breach of contracts with customers

Under both NUS, the applicant expects to receive claims from customers (laboratories, hospitals, etc.) for compensation for breach of contracts. The applicant explains that these are difficult to estimate, as there is a large variety of contractual arrangements. Additionally, customer claims may be based on contractually defined penalties, but are not limited to them. Claims could be made for any incurred damages. The costs calculated are therefore expected by the applicant to be a rough indication of the costs of potential claims and could be much higher.

Under NUS1, the applicant estimates costs for affected assays not sold (calculated based on sales price as an approximation), until customers are expected to have switched to a new system (maximum 2 years). The costs of the switch to a new instrument are also expected to be part of the claim, and are calculated based on the market price of new instruments.

Under NUS2, only costs for affected assays not sold are taken into account, expected until substitution takes place and the products become available again.

On the request of SEAC the applicant provided a non-confidential range for the expected cost of breach of contracts with customers under the Non-Use Scenarios, again calculated for Uses 2 and 3 combined:

- If competitors can take over the applicant's market share fully (NUS1), costs are estimated at €550 million to €5.5 billion
- If competitors are unable to take over the applicant's market share (NUS2), foregone profits are estimated at €50 million to €5 billion.

These are all present values over the requested review period.

Social cost of unemployment:

According to the applicant, the NUS would lead to job losses as a result of the closure of production lines or below-capacity use of production lines resulting in job redundancy in production as well as in supporting functions.

The applicant has calculated social costs of unemployment for NUS2 (competitors unable to take over the applicant's market share) with all substitutions delayed till the end of the review period, and based only on the 414 FTE jobs directly affected, which are expected to be lost (jobs lost in supporting functions are not included). This corresponds to €42 million welfare loss (present value), and this number has been calculated using the methodology recommended by SEAC. These estimates apply to Uses 2, 3 and 4 combined.

The applicant does not calculate the social cost of unemployment for the other NUS, but describes how they would compare to the scenario described in the previous paragraph (substitutions delayed till the end of the review period and competitors unable to take over the applicant's market share). In the scenario with substitutions delayed till the end of the review period and competitors able to take over the applicant's market share, job losses would be higher. In the scenarios with substitutions completed as planned (regardless of whether competitors are able or not to take over the applicant's market share), a lower number of jobs than estimated above are expected to be lost.

Impact on patients:

The applicant expects that there would be increased healthcare costs and related costs due to the temporary unavailability of affected IVD assays. This impact would occur for at least one but possibly seven years, depending on the NUS.

The applicant provides a qualitative description of the positive health impacts related to the

use of IVD assays. These are, in general:

- Finding the right treatment for the patient – better outcomes and recovery times
- Early diagnosis – preventing illness from developing, slowing down disease
- Monitoring of those with ongoing diseases – reducing risk of complications.

The applicant also provides more detailed descriptions of the benefits to society of each of the products affected in Table 12 of their SEA document.

The applicant describes that a large number of patients could potentially be affected by non-authorisation, as the number of tests performed with the affected assays is 2-3 billion per year worldwide for Uses 2, 3 and 4 combined, of which approximately half take place in the EEA. Assuming some 10 tests per patient, this would represent 100-150 million patients affected per year in the EEA (for Uses 2, 3 and 4 combined).

The applicant explains that monetisation of benefits to patients is not possible, mainly due to the lack of cost-utility analysis for individual assays. Instead, they provide some illustrative calculations to demonstrate the minimum scale of the potential impacts.

To do this, the applicant takes an arbitrary amount (the estimate for maximum possible lost profits for all 3 uses: a confidential number, with a non-confidential range of €700 million to €7.0 billion), and calculates what is the minimum efficiency their affected IVD assays would have to have for the impact on patients to be at least that arbitrary amount every year. This is done using a Value of a Statistical Life (VSL) of €1.5 million and a Value of a Life-Year (VOLY) of €80 000 (2021 prices).

The result they arrive at is that, as long as 1 in 20 000 of the affected tests are effective enough to prevent the loss of 1 Quality-Adjusted Life Year (QALY), or 1 in 380 000 of the affected tests are effective enough to prevent one premature death, the impacts on patients every year would be higher than the arbitrary number picked. The applicant considers that, given the importance of the affected tests (supported by the qualitative descriptions provided), it is likely that the effectiveness of the tests in preventing detrimental health outcomes is much higher than that.

In conclusion, the applicant estimates an impact on patients of at least €700 million to €7.0 billion per year for all 3 uses that would be avoided under the applied for use scenario. They further disaggregate this figure for Uses 2 and 3 combined based on the assays affected by each use, estimating a value of €500 million to €5.0 billion per year.

Table 4: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts [annualised to € million per year]
1. Benefits to the applicant and/or their supply chain	
1.1 Avoided profit loss due to investment and/or production costs related to the adoption of an alternative	Not applicable
1.2 Avoided profit loss due to ceasing the use applied for	Quantified, but not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions
1.3 Avoided relocation or closure cost	Not applicable
1.4 Avoided residual value of capital	Not applicable
1.5 Avoided additional cost for transportation, quality testing, etc.	Quantified costs for breach of contracts with customers, but not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions

Sum of benefits to the applicant and / or their supply chain	Quantified, but not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions
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[8]	Quantified, but not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions
2.2 Foregone spill-over impact on surplus of alternative producers	0 (substitution would occur both under the AfU scenario and NUS)
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	At least €500 million to €5.0 billion in avoided impacts on patients
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	At least €500 million to €5.0 billion
3. Aggregated socio-economic benefits (1+2)	At least €500 million to €5.0 billion

5.3. Combined assessment of impacts

The applicant considers that impacts on patients are likely to be the main impact of non-authorisation, and uses only that impact when calculating the cost of abating the emission of one kg of 4-tert-OPnEO/4-NPnEO.

The applicant calculates that measure for Uses 2 and 3 combined, resulting in €2-44 million (non-confidential range) per kg of OP_{equiv} or NP_{equiv} abated. This is calculated based on releases if substitutions are completed as planned. If the releases of OP_{equiv} or NP_{equiv} are converted into 4-tert-OPnEO and 4-NPnEO using a conversion factor derived from the release rates reported in the CSR, the cost per kg range would be €0.7-15 million.

SEAC notes that if this figure were calculated based on the year of maximum releases, assuming all releases are delayed till the end of the review period (approximately 560 kg of 4-tert-OPnEO and 4-NPnEO combined; note that the figure rounds up to the same whether only Use 3 or Uses 2 and 3 combined are considered), the cost per kg of releases abated would still be within the non-confidential range presented by the applicant above. Using 560 kg/year of releases of 4-tert-OPnEO and 4-NPnEO for this use could be considered a worst-case scenario.

SEAC agrees with the applicant that it is not necessary to calculate a corresponding figure solely for the releases narrowly associated with the use of the IVD kits by downstream users in the EU (Use 3) (excluding those associated with the formulation and filling of the IVD kits (Use 2)), due to the small relative amount of the latter compared to the former.

Additionally, SEAC notes that it could be useful to also consider the releases in the context of the total scale of the applicant's operation. The applicant reports that > 10 000 of their instruments are used across the EEA. Allocating the maximum release estimate of 560 kg of 4-tert-OPnEO and 4-NPnEO combined to these instruments suggests that the average annual release per instrument would be less than 60 g of 4-tert-OPnEO and 4-NPnEO combined. Additionally, the applicant reports that 500 million to 1.0 billion tests per year are performed in the EEA using the IVD assays affected. Correspondingly, the average release of 4-tert-OPnEO and 4-NPnEO combined per test amounts to 0.5-1 mg.

[8] 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).

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

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits [annualised to € million per year]	At least €500 million to €5.0 billion in avoided impacts on patients (also quantified avoided foregone profits, avoided costs for breach of contract and avoided social costs of unemployment, which are not considered by the applicant in the calculation of cost of non-use per kg of prevented emissions)	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	Not applicable	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 associated with the direct release of 524 kg of 4-tert-OPnEO and 32 kg of 4-NPnEO in the year of maximum releases
Summary of socio-economic benefits	**At least €500 million to €5.0 billion in avoided impacts on patients** **+ avoided foregone profits** **+avoided costs for breach of contracts** **+avoided social costs of unemployment** **+avoided impacts on hospitals beyond the costs of claims for breach of contract**	**Summary of excess risk**	**Risks associated with the direct release of 524 kg of 4-tert-OPnEO and 32 kg of 4-NPnEO in the year of maximum releases**

Table 6: Cost of non-use per kg

Total cost (€) per year (Uses 2 and 3 combined)	500 million to 5.0 billion
Total emissions (kg) per year (maximum, Uses 2 and 3 combined)	560 4-tert-OPnEO and 4-NPnEO combined
Ratio (€/kg)	0.7-15 million

5.4. SEAC's view on Socio-economic analysis

SEAC notes that the applicant's socio-economic analysis was performed for Uses 2, 3 and 4 together. Although some differentiation was made for Use 4, Uses 2 and 3 were analysed together, as the applicant considers the impacts are the same whether an assay cannot be produced (Use 2) or cannot be used by customers (Use 3). The underlying assumption seems to be that authorisation would be granted for all uses or for none of them.

SEAC asked the applicant whether, in the case an authorisation were granted for Use 2 but not for Use 3, exports to the EEA could not continue under the NUS (SEAC notes that foregone profits based on the non-EEA market are calculated by the applicant to be higher than for the EEA market). The applicant acknowledged that this is correct, but noted that detailed figures were provided that differentiated products sold in EEA and non-EEA countries and concluded that total impacts for the eventuality that Use 2 were authorised but not Use 3 could be calculated from the information provided. Additionally, they noted that their conclusion that the benefits of continued use of 4-tert-OPnEO and 4-NPnEO associated with Uses 2 and 3 outweigh the remaining risks to the environment are based only on the calculated minimum impacts on patients. SEAC concurs with the applicant's point and considers that the information provided by the applicant is sufficient.

The applicant provides a very detailed and transparent description of the methodology used to calculate the different impacts, which allows SEAC to fully understand the assumptions behind the calculations and come to a conclusion regarding their reliability.

SEAC considers that the methodology used to calculate foregone profits was appropriate and provides a good indication of the scale of the potential impacts of non-authorisation. It notes that the different categories of foregone profits have different levels of uncertainty, with the estimates of lost profits arising from foregone growth being less reliable.

SEAC concurs with the applicant's assessment of which parts of foregone profits may represent distributional impacts and which may represent a genuine loss of producer surplus. However, especially for NUS2, where foregone profits are estimated to occur for several years, SEAC notes that changes in profits made by the applicant do not necessary reflect changes in economic surplus across the EU economy, so the net loss of economic surplus may be lower.

SEAC considers that the applicant's estimates for the minimum potential cost of claims brought by customers for breach of contract are an appropriate measure of the likely minimum scale of the impact. SEAC notes that in the event of an authorisation being granted for Use 2 and not Use 3, it is possible that the applicant would not be in breach of their contract with its downstream users. However, this will depend on the exact contractual arrangements.

The approach used by the applicant to monetise the welfare loss associated with the unemployment of some of their workers follows the SEAC note on the social cost of unemployment (see footnote 8). SEAC considers that this impact would present a significant welfare loss and can be considered a significant benefit of continued use. SEAC further notes that the estimated cost is for Uses 2, 3 and 4 combined, and that the exclusion of indirectly affected jobs from the calculations is likely to result in an underestimate of this impact.

The applicant considers that the impact on patients is likely to be the main impact of non-authorisation, and SEAC concurs with that conclusion. SEAC acknowledges the difficulties involved in quantifying that impact, and considers that the methodology used by the applicant to provide an approximation of the minimum scale of this impact is an appropriate one, and a good way to overcome the issue of the lack of data. SEAC agrees that the conclusion that impacts on patients are at least the amount claimed is a credible one.

SEAC notes that this impact on patients is characterised by the applicant as an increase in healthcare costs, whereas the estimates used for the VOLY and VSL (which come from a source SEAC considers credible) cover a much wider variety of impacts to society, including the patients' wellbeing. However, this does not affect the applicant's conclusions.

Due to the use of a quantified amount for impacts on patients that is very likely to be an underestimate, as well as the exclusion of several impacts from the cost-effectiveness calculation, including some that could be at least as high as the amount quantified for impact on patients, SEAC considers that the applicant's estimate of the cost per kg of emissions prevented is likely to be underestimated.

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 in response to questions from SEAC and RAC,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☒ Normal (7 years)

☐ Long (12 years)

☐ Short (…. years)

☐ Other: _____ years

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

6.1 RAC's advice

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

6.2. Substitution and socio-economic considerations

The applicant requests a review period of 7 years in order to develop, implement and obtain regulatory approval for alternatives for the different IVD assays included in the use applied for. Based on the information provided by the applicant, SEAC takes the following considerations into account:

- There are no technically feasible alternatives to implement by the sunset date.
- The applicant has performed research and development to find alternatives to 4-tert-OPnEO/4-NPnEO. Although substitution has been completed already for several assays, and is expected to be completed for others before the sunset date, so far for several IVD assays, the alternatives have either not achieved comparable performance across key requirements or several steps remain before substitution can be fully implemented (such as development, regulatory approval and production). SEAC concurs that alternatives could not be fully implemented before a period of 7 years from the sunset date.
- The substitution plan is clear and leads to no doubts about the timeline needed.
- No information concerning potential alternatives was received during the public consultation
- The negative impacts to society of not granting an authorisation that would allow continued use. It is considered as credible by SEAC that impacts on patients will be at least the amount quantified by the applicant, and SEAC concurs that there would likely be additional impacts to the applicant and its employees.

Taking into account these points, SEAC recommends a **7**-year review period.

7. Proposed additional conditions for the authorisation

Were additional conditions[9] proposed for the authorisation?

☒ Yes

☐ No

7.1 Description

RAC

Proposed additional conditions

The applicant shall follow the substitution activities described in the application.

[9] 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.

SEAC

Proposed additional conditions

None

7.2. Justification

RAC considers that the applicant has not demonstrated that OCs and RMMs are appropriate and effective in limiting the risk to the environment.

RAC takes note of SEAC's views that the applicant's ongoing and planned substitution activities are well-described and that the plans presented by the applicant are appropriate to achieving substitution in the review period applied for, with most substitutions being achieved in the first few years. Total yearly releases are therefore expected to steeply decline already in the two years immediately after the sunset date. Therefore, it is necessary to follow the substitution activities described in the application.

RAC further notes that implementing further RMMs (collection of liquid waste for adequate treatment) would likely take a significant amount of time, which would result in most substitutions having been achieved before the additional RMMs can be implemented.

Under these specific circumstances, RAC recommends that a condition for the authorisation requiring downstream users to collect liquid wastes for adequate treatment should not be imposed in this case.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[10] proposed for the authorisation?

☐ Yes

☒ No

8.1 Description

Not applicable

8.2 Justification

Not applicable

[10] 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. Recommendations for the review report

Were recommendations for the review report made?

☐ Yes

☒ No

9.1 Description

Not applicable

9.2 Justifications

Not applicable

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

Annex 1: Status of R&D

This annex includes more details regarding the status of R&D the different products included in the use applied for.

1) Clinical chemistry (CC)

The substitution process for the CC assays has started in 2016. The applicant has already found an alternative for product CC1 and substitution will be achieved before the sunset date. The applicant has also identified alternatives for CC2, CC3, CC5 and CC7. 3 alternatives have been identified for CC6 and testing is ongoing to identify the best alternative. The expected timelines for substitution is foreseen between the beginning of 2019 and end of the year. Longer timeline are expected for CC7 and CC8 due to technical challenges. Replacement projects are running at the applicant's site but delays can occur at any time if technical difficulties are encountered. The applicant has provided the example of CC5 where a problem happened due to an interaction between the new surfactant and the preservative. Further testing was required and new tests with another preservative were necessary. The applicant estimates that the final CC products will be substituted by the end of 2026.

2) Drug Monitoring (DM)

For these products, a change of the surfactant in reagents as well as in the production process of the latex beads conjugated with antibodies are necessary. The production process of the beads is covered by the Use 4. Since the 2 processes are highly interlinked, the substitution is rendered more difficult. The applicant details the necessary steps that need to be achieved to accomplish the substitution. If the market authorisation is modified as a major change, the minimal time required would be between 5 to 8 years due to differences in shelf-life. If a complete re-registration is need for the market authorisation, a longer timeline would apply.

The applicant has already substituted DM1 and it is therefore not covered by this AfA. Substitutions of DM2 and DM3 are expected to take place before the sunset date, too. Technical difficulties that will require more time have been encountered by the applicant in some products. A total timeline for substitution of 5 to 8 years is expected. Several assays are tested in parallel, and to what extend this can happen depends on the number of available workforce. Including the risk of delay, the substitution process for all DM assays including introduction to the market and use of the current stock of assays containing 4-tert-OPnEO/4-NPnEO at customers' sites may last until end of 2026.

3) HIV

HIV diagnostic assays are subject to very strict regulations and if any change in the composition or production is introduced, they need to be thoroughly tested. Therefore, a silent change is considered not possible by the applicant. Moreover, clinical validation studies on blood banks and routine samples worldwide are required. Validation of the assays and market authorisation by the respective health authorities are expected to take several years. After a period required to obtain the market authorisation, introduction to the market of the updated HIV assay is estimated by Q4 2025 taking into account potential technical and regulatory risks.

A new analyser is being introduced stepwise by Roche. In general, after the introduction of the new generation instruments, 5 years of support (including the supply of IVD assays) is required.

4) Blood GAS and Electrolyte Analysis

The HB CALIBRATOR is needed for measuring haemoglobins and bilirubin on a specific system (cobas® b 221). Since this system and the corresponding test are planned to be removed from

the market because of the new IVD and REACH regulations, support is planned to end at a confidential date in the next years. The replacement of the system by an alternative is not feasible for the moment since the alternative is not designed to perform the same tasks. The other system addresses premium needs and is not designed to perform large number of samples per day, as the current one.

Nevertheless, in order to enable customers to find suitable alternative systems based on their needs, supply until the planned date of removal needs to be ensured. If not, contractual penalties and compensation claims would have to be paid by the applicant if the system is removed before the end of existing contracts.

Regarding the activities associated with replacement of 4-tert-OPnEO in the HB CALIBRATOR, efforts have started in 2016, when feasibility for replacement material compatibility and wetting compatibility could be demonstrated. The applicant estimates the time needed for substitution as between 5 to 7.5 years. But since the current system would need to be removed from the European market before that, the applicant states that it is not economically viable to replace 4-tert-OPnEO before the removal from the market of the analysis system since it would need large efforts in verification, implementation in production and change registration in China. Finally, it is not certain that the replacement would be achieved before the removal from the market.

In conclusion, the applicant needs the authorisation only to supply the product until the deadline of removal of the products from the EU market.

5) Accutrend®

The applicant foresees a silent change for this product group. They state that they expect the substitution will be achieved before the sunset date, but require authorisation in case of technical difficulties or failure to complete the validation in the planned timeframe.

Indeed, if no unexpected delay occurs and the change fulfils the validation criteria, replacement is planned to be achieved by the Q3 2019. To this timeline, 18 months have to be added due to shelf life of the old products to enable customers who have purchased the last products on the market to use up their stocks, leading to a complete replacement by end of Q1 2021. If technical difficulties occur, this date could be delayed by 24 months.

6) Urinalysis

The applicant foresees a silent change for this product group. They state that they expect the substitution will be achieved before the sunset date, but require authorisation in case of technical difficulties or failure to complete the validation in the planned timeframe. The alternative has already been identified, validation is ongoing and if no unexpected delay occurs and the test strips fulfil the validation criteria, the replacement is planned to be finished by end of Q3 2020. To this date, 24 months have to be added due to shelf life of the old products to enable customers who have purchased the last products on the market to use up their stocks. If technical difficulties occur, this date could be delayed to end of Q3 2025.

7) Subgroup RMD1 and 2

RMD1: The applicant foresees a complete re-registration of the product since a new version of the assay is being developed free of 4-tert-OPnEO. Feasibility studies are ongoing for the new assay, and three possible alternatives have been proposed. Following the validation/verification studies and clinical validation studies, the 4-tert-OPnEO-free assay is planned to be available in 2021. Replacement of the existing assay on the market should be achieved by Q3 2022. The probability of completing the replacement in the planned timeframe is estimated at 90 % by the applicant. If technical difficulties occur, this date could be delayed

by 24 months.

RMD2: The applicant foresees a silent change for this group. Many replacement steps are foreseen to be finished before the sunset date, but the applicant states that authorisation is still necessary during clinical validations, subsequent regulatory and market approvals, and in case of unexpected delay due to technical difficulties. Two alternatives have been identified, and feasibility tests using these alternatives are ongoing. Replacement of the assay is planned to be completed in 2021/2022. The applicant state that the likelihood of finishing the replacement in time is high.

8) Roche Tissue Diagnostics

The applicant foresees a silent change for this group. Testing without surfactant at all was performed but this negatively impacted the in situ hybridisation staining, and therefore this approach was rejected. One alternative was selected based on the feasibility studies. Currently, three concentrations are being tested in ongoing stability studies. It is expected to be completed by Q1 2020 (95 % confidence). Distributed product will expire by Q1 2022 (shelf-life). If technical difficulties occur, this date could be delayed by 36 months.