Application for Authorisation

UK REACH

ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

Public version

Legal name of applicant(s):	Siemens Healthcare Diagnostics Products GmbH (Marburg Germany).
Submitted by:	Siemens Healthcare Diagnostics Products Ltd. (Llanberis UK, Only Representative)
Substance:	Entry #12: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (Triton™ X-100, Triton™ X-405)
Use title:	1: Use of IVD kit reagents on diagnostic analyser systems by professional users 2: Use of IVD wash solutions on diagnostic analyser systems by professional users

Note

This complete version of this document includes some text and figures that are highlighted in grey. These parts of text have been blanked out in the public version of this document. Justification for confidentiality claims is provided in Section 8 of the present document.

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List of Abbreviations

4-tert-OP	4-tert-Octylphenol / 4-(1,1,3,3-tetramethylbutyl)phenol
[redacted]	#D (table, unless otherwise stated)
AfA	Application for Authorisation
[redacted]	[redacted]
[redacted]	[redacted]
AoA	Analysis of Alternatives
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ca.	circa
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAI	Chemistry, Automation & Informatics
CARACAL	Competent Authorities for REACH and CLP
CC	Clinical chemistry
CE-mark	Conformité Européene (mark)
[redacted]	[redacted]
CIA	Change Impact Assessment
[redacted]	[redacted]
[redacted]	[redacted]
CLP	Classification Labelling and Packaging regulation
CMC	Critical Micelle Concentration
[redacted]	[redacted]

COD	Chemical oxygen demand
[redacted]	[redacted]
CRB	Change Review Board
CSF	Cerebrospinal fluid
CSR	Chemical Safety Report
[redacted]	[redacted]
DCP	Design Change Process
DfE	Design for the Environment
[redacted]	[redacted]
[redacted]	[redacted]
DMR	Device Master Record
[redacted]	[redacted]
[redacted]	[redacted]
ECHA	European Chemicals Agency
EDC	European Distribution Centre
[redacted]	[redacted]
EEA / non-EEA	European Economic Area
EFTA	European free trade association
EHS	Environment, Health & Safety
ELISA	Enzyme-linked Immunosorbent Assay
[redacted]	[redacted]
EO	Ethylene oxide
EPA	Environmental Protection Agency (US)
[redacted]	[redacted]
EQS	Environmental Quality Standards
EU	European Union
EUSES	European Union System for the Evaluation of Substances
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration (US)
[redacted]	[redacted]
FTE	Full-Time Equivalent
[redacted]	[redacted]
GmbH	Gesellschaft mit beschränkter Haftung
[redacted]	[redacted]

[redacted]	[redacted]
IFU	Instruction for Use
[redacted]	[redacted]
[redacted]	[redacted]
IVD	In-Vitro Diagnostic
IVDR	In-vitro diagnostic medical device regulation
kg	kilogram
kg/y	kilograms per year
[redacted]	[redacted]
[redacted]	[redacted]
LD	Laboratory diagnostics
LoB	Limit of Blank
LoD	Limit of Detection
LoQ	Limit of Quantification
MA	Massachusetts
MDX	Molecular Diagnostics
µg/litre (µg/L)	Micrograms per litre
µg/kg	Micrograms per kilogram
mg/kg dw	milligrams per kilogram dry weight
[redacted]	[redacted]
NSB	Non-specific binding
[redacted]	[redacted]
OEM	Original Equipment manufacturer
OP	Octylphenol
OPE, OP/E, OPnEO	Octylphenol ethoxylate
[redacted]	[redacted]
PBT/vPvB	Persistent, Bioaccumulative and Toxic Substances/very Persistent and very Bioaccumulative
PCR	Polymerase chain reaction
PDP	Product Development Process
PEC	Predicted Environmental concentration
PHT	Product Health Team
POC	Point of Care
ppm	parts per million
[redacted]	[redacted]

[redacted]	[redacted]
Q&A	Question and Answer
RA	Regulatory Affairs
RAC	Committee for risk assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
R&D	Research and development
RG	Report generation
[redacted]	[redacted]
[redacted]	[redacted]
SAP (ID)	Systems Applications and Products Identification
SCM	Supply Chain Management
SEA	Socio Economic Analysis
SEAC	Committee for socio-economic analysis
[redacted]	[redacted]
STP	Sewage Treatment Plant
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
WTP	Willingness to pay
WWTP	Wastewater Treatment Plant
4-tert-OP	4-tert-Octylphenol / 4-(1,1,3,3-tetramethylbutyl)phenol

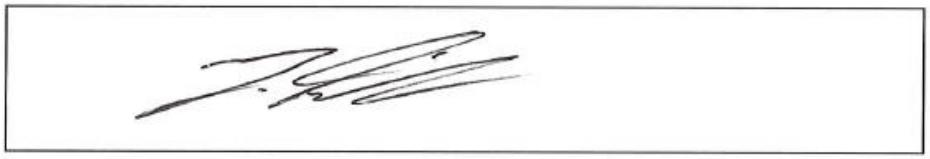
DECLARATION

We, Siemens Healthcare Diagnostics Products Ltd as Only Representative on behalf of Siemens Healthcare Diagnostics Products GmbH, request that the information blanked out in the "public version" of the Analysis of Alternatives and Socio-economic analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (21.06.2022) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature:

[Fraser Logue, VP Operations]

Signature:



[Joerg Fischer, Finance Director]

1 Summary

1.1 Introduction

Siemens Healthcare Diagnostics Products Ltd (in the following referred to as Siemens Llanberis) is acting as the Only Representative for UK REACH purposes for Siemens Healthcare Diagnostics Products GmbH (hereinafter referred to as Siemens Marburg). They are both part of Siemens Healthineers AG which is a globally operating holding company, which also encompasses the Siemens Healthineers European Distribution Centre (EDC) in Duisburg, Germany as part of the Siemens Healthcare Diagnostics Products GmbH. The EDC distributes annually more than #D in-vitro diagnostic (IVD) products (kit reagents and wash solutions), some of which contain either 4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol (trade name **Triton™ X-100**), or (Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy- (trade name **Triton™ X-405**) in typically low concentrations to >100 UK customers. These two substances fall within the group of ethoxylates of 4-tert-octylphenol (4-tert-OP) and the present AfA covers the downstream use of these IVD products, namely:

- **Use #1**: Use of IVD kit reagents on diagnostic analyser systems (# A (range: 75-200) IVD products), and
- **Use #2**: Use of IVD wash solutions on diagnostic analyser systems (# A (range: 1-10) IVD products).

The "Applied for Use" involves the application of Triton™ X-100 as a cleaning agent (detergent) and stabiliser in both Applied for Uses. Triton™ X-405 is also used as a cleaning agent (detergent) and stabiliser in Use #1 only. These IVD products are used by hospitals, commercial laboratories and research centres on several Siemens Healthineers and third-party analysers to perform vital diagnoses of specific diseases and conditions in patient samples.

Siemens Llanberis as the OR for Siemens Marburg is seeking Authorisation of the Applied for Uses on behalf of downstream users in the UK. Authorisation is being sought for 12 years for Use #1 and 5 years for Use #2 from the sunset date (January 4, 2021). This is vital to allow the continued use of the aforementioned IVD products while efforts for phasing out the use of OPEs continue.

1.2 Availability and suitability of alternatives

Alternatives considered for downstream users in this document include alternative IVD products and third-party analysers available on the market. While it is not possible for the applicant to have a full overview of whether they are OPE-free and deliver the same diagnostic capabilities, for the purposes of the present analysis it is optimistically assumed that such alternatives exist on the market. As such, it is assumed in the event of non-Authorisation, downstream users of OPEs would aim to switch to alternative third-party analysers in order to minimise disruption to their provision of diagnostic services, although this in itself would represent significant disruption and cost for those downstream users.

In addition to the following economic consequences for the applicant, it must be emphasised first and foremost that the non-continuation of the uses will at high-risk result in an at least temporary loss of diagnostics in the context of serious diseases (e.g. several cancers, pregnancy conditions,

blood, liver, kidney and bone diseases, heart conditions, hormonal imbalances, COVID-19 and aid of fertility treatments). This cannot be directly expressed in monetary parameters, but may lead to sub-optimal treatment of thousands of patients and is the most important argument for continuing the uses for the requested period.

The cost of premature replacement of the Siemens Healthineers analysers has been estimated at #E (range: £10 – 25 million, 2021 prices). This estimate does not account for the indirect cost and disruption caused by a switch to a new analyser, which typically takes 6-24 months to complete and during which time there would be significant impacts on the diagnostic testing of patient samples in UK hospitals and laboratories. It should also be understood that, in practical terms, switching to a new analyser platform would depend on the availability of the same range of tests on the new platform. Switching could thus mean that hospitals and labs might need to invest in a multitude of different analysers which would need to be placed within a limited amount space and would require additional human resources and training.

On the other hand, in terms of alternative substance and technologies that could be used to substitute OPEs in the manufacture of the IVD products that fall within the scope of the two Applied for Uses, since 2013, Siemens Healthineers implemented a policy to prevent the use of OPEs in any new product development where technically feasible. This requires extensive research work, reaching out to authorities and commissioning consultants, to identify alternatives which ensure that the diagnostic kits function effectively and deliver accurate patient results.

Globally, Siemens Healthineers is the manufacturer of over # A (range: 50-500) existing products, across # A (range: 10-25) different product lines, where OPEs are used and which are in the scope of REACH Authorisation (at the time of its EU REACH Application for Authorisation (AfA), Siemens had #D (range: 100-1,000) IVD products containing OPEs. This demonstrates the level of effort being placed into reformulation). Reformulating products to replace OPE must be done on a 'per product' basis as the technical properties of OPE, which make a diagnostic product function effectively and meet specific performance parameters, will differ between products. The only effective and compliant method of identifying an alternative is to perform feasibility testing with a number of selected substances with similar properties on a 'per product' basis to conclude which of these alternatives performs to the same repeatable standard as OPE. This must be done with the initiation of a Product Development or Design Change Project, processes strictly regulated under the EU In-Vitro Diagnostic Regulation 2017/746, as well as other global regulations. As a result, there is no single specific alternative substance or combination thereof which Siemens Healthineers could presently switch to for the purposes of any of the two Applied for Uses.

Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched an extensive Substitution Plan. The estimated cost of reformulation for all the original OPE-containing products is #F (range: €10-100 million) and with significant R&D resource involved.

With particular regard to the present two Applied for Uses, Siemens Healthineers has reformulation and phase out projects (covering multiple OPE-based formulations) underway which are estimated to reach completion between end 2032/3 (for Use #1) and end 2025 (for Use #2).

1.3 Socio-economic benefits from continued use

The continued use of Triton™ X-100 and Triton™ X-405 over the period to 2033 (Use #1) and end 2025 (Use #2) will confer significant socio-economic benefits within and outside Siemens Marburg's supply chain. These can be summarised as follows:

- Critically, healthcare providers and patients in the UK will continue to have access to the #D relevant IVD kit reagents (use #1); also importantly, the continued use of the #D OPE-containing IVD wash solution products (use #2) distributed by the Siemens Healthineers' EDC will allow the continued operation of #C, D analysers which each allows the use of tens of different assays. The number of tests undertaken on the impacted analysers each year in the UK extends to millions. These analyser systems enable tests for detection of multiple health conditions and support the early diagnosis of numerous diseases, including life-threatening ones (e.g. several cancers), pregnancy conditions, blood, liver, kidney and bone diseases, heart conditions and hormonal imbalances and aid fertility treatments. Patients who cannot undergo vital tests within the required timeframe will be significantly adversely affected; this is one of the reasons the IVD industry is so strictly regulated, to ensure healthcare providers can rely on the performance and supply of products, including the delivery of timely results.
- Users of #A different analyser models will continue to have access to the full range of IVD kits and wash solutions made in Marburg, elsewhere in the EEA (by OEM suppliers) and the USA and Asia (by Siemens Healthineers and OEM suppliers) and will thus avoid (a) operating costs increase from outsourcing of diagnostic testing, (b) the cost of selection, validation and installation of third-party analysers/kits and (c) the cost of premature replacement of their existing analysers. The cost of replacing a platform is therefore only a part of these costs at an average £50,000 per unit; many hospitals and laboratories will run multiple analysers. As noted above, the overall capital costs for downstream users is estimated at ca. #E million (range: £10 - 25 million);
- Siemens Marburg and Siemens Healthineers will be allowed to continue the manufacture of multiple OPE-containing IVD kit reagents and wash solutions while reformulation and phase out takes place. It would also avoid potential indirect adverse impacts on the sales of numerous OPE-independent kits that rely on continued use of the Use #2 wash solutions, and which are used on the same analysers as the OPE-dependent IVD kits. The estimated total present value profit losses across all affected products equate to around #E million (range: £10 to 100 million).

[redacted]

- Suppliers to all Siemens Healthineers operations identified above will continue to generate profits from associated sales of raw materials and services.

The proportion of socio-economic benefits from continued use of OPEs in the Applied for Uses that can be monetised amounts to #E million (range: £10 – 100 million) for Use #1 (2022-2033 Present Value, 3.5% discount), and #E million (range: £1-10 million) for Use #2 (2021-2025, Present Value, 3.5% discount).

1.4 Residual risk to the environment of continued use

Given the large number of users of OPE-containing IVD products and the likely variability of Risk Management Measures (RMM) in place, the CSR accompanying this AfA makes conservative assumptions as regards the releases of OPEs/4-tert-OP to the environment. More specifically, it is conservatively assumed that the entirety of OPEs placed on the market by Siemens is released into wastewater which is directed to local municipal Sewage Treatment Plants (STPs). Thereafter, 26.5% of total Triton™ X-100 and 9.5% of Triton™ X-405 input is assumed to be emitted to the aquatic environment as 4-tert-OP, while 3.45% of total Triton™ X-100 and 1.22% of Triton™ X-405 input is assumed to end up in sludge as 4-tert-OP. 53% of this sludge is assumed to be applied to agricultural soil or sent to compost. Over the requested review periods, the releases of 4-tert-OP to the environment account for a total of ca. #A,J (range: 10-100) kg for Use #1 and #A,J (range: 100-500) kg for Use #2, when assuming a worst-case scenario.

Environmental 4-tert-OP concentrations calculated for the local scenarios due to the wide dispersive Use #1 and #2 are below the EQS-values derived under the Water Framework Directive, which have been used as the values for risk characterisation. For Use #2 local PECs are higher, about a factor of 3 lower than the EQS values, but only for the period 2021-2025; thereafter, wash solutions relevant to the #D will reach their end of life and thus the very conservative assumptions made in the CSR calculations will no longer apply. As a result, PECs for all compartments will dramatically decline. On the regional scale the calculated aquatic PECs are over 100 times lower than the relevant EQS. Thus, adverse effects for water and sediment organisms are less probable than in the local scenario. The assumptions made in the CSR are generally conservative. Therefore, average concentrations are expected to be lower than those indicated in the local assessment.
Comparison of socio-economic benefits and residual risks

The ratio of the total cost of non-Authorisation (i.e. the benefit of continued use) and the total emission of 4-tert-OP to the environment is:

- **Use #1**: #E (range: £100k – 2.5 million) per kg of 4-tert-OP released over the period 2022 -2033; and

- **Use #2**: #E (range: £10k -100k) per kg of 4-tert-OP released over the period 2022 -2025.

The above estimates are significant underestimates of the actual benefits conferred by the continued use of OPEs in the Applied for Uses as they only encompass benefits that could be readily quantified and monetised. The true benefit-cost ratios must be assumed to also encompass:

- The significant benefits to the health of numerous patients across the UK who are diagnosed with or monitored for a wide range of diseases through the use of #C,D tests that contain OPEs or require the regular use of OPE-containing wash solutions on the relevant analysers and which are placed on the market by Siemens Marburg;

- Manufacturers of OEM IVD products and analysers (those made on behalf of Siemens Healthineers and other, third-party ones) would continue to earn profits;

- The profits for Siemens Healthineers from sales of IVD products would be maintained while it carried out its reformulation programme of activities and analysers that might potentially be indirectly impacted if the continued use of OPE-containing IVD products within the UK was not

authorised and thus Siemens Healthineers would suffer loss of economies of scale and global reputational damage; and

- The significant cost impacts on healthcare provision, operational disruption, inconvenience for a period of a minimum 6 months (but potentially as high as 24 months) which the users of Siemens Healthineers analysers would avoid, as they would avert the premature replacement of their units.

In addition, the monetised benefits that have been presented above have been discounted over time, whilst the physical quantities of 4-tert-OP released under the Applied for Uses have not.

1.5 Factors to be considered when defining the operating conditions, risk management measures, and/or monitoring arrangements

This AoA-SEA document demonstrates that the current practices of the downstream users of OPEs with regard to the treatment of their OPE-containing wastewater are in accordance with existing UK legislation. Efforts to implement additional Risk Management Measures such as the segregation and incineration of OPE-containing wastewater would face significant technical, practical and logistical challenges, which are described In Appendix 2. In addition, the cost of treating this waste would be disproportionate. Appendix 2 demonstrates that even for those downstream users whose wastewater has a higher concentration of OPEs (but still in the <0.01% range), the cost of incineration alone (i.e. excluding on-off investment costs that would be in the range of thousands of pounds) would exceed £ #E (range: £50,000-100,000) per kg 4-tert-OP release avoided. This cost ratio will certainly be much higher for smaller operators with lower consumption of OPE and much lower OPE concentration in their diagnostic analyser wastewater.

It is therefore considered that a move to segregation of wastewater for all customers would produce significant financial and logistical issues for a significant proportion of healthcare institutions in the UK. Minimisation of emissions via phase out of OPEs in IVD products is a far more viable and cost-effective route, albeit this also involves significant costs and R&D resource over the coming years.

1.6 Factors to be considered when assessing the duration of a review period

Siemens Marburg's AfA meets the requirements set out by the ECHA Committees for Authorisation review periods longer than normal (7 years), as follows:

- An Authorisation of appropriate length is fundamental for the continued operation of the downstream user facilities. Siemens Healthineers is investing a significant amount of resources and funding towards the phase out of OPEs from a substantial number of IVD products. The cost of Siemens Healthineers' Substitution Plan exceeds £ #F (range: €10-100 million). This substantial expenditure is #F .

- The premature replacement of Siemens Healthineers analysers would impact [redacted] (range: 100-1,000) analysers which are relevant to Applied for Uses #1 and #2. The overall present value cost of the premature replacement of Siemens Healthineers analysers is ca. [redacted] (range: £10-25 million, 2021 prices). This figure does not encompass the cost and inconvenience of a 6–24-month disruption of the performance of medically critical IVD tests while the switch to a third-party analyser occurs, assuming that such a switch would be feasible in practice;

- Reformulation of the IVD products that depend on OPEs might include a range of costs, such as (a) Internal R&D (reformulation) cost; (b) Internal re-registration submission preparation cost; (c) Re-registration fees; and (d) downtime losses. The latter would be the most critical. There is no simple or single drop-in replacement for OPEs in Siemens Healthineers manufacturing processes. In the absence of a REACH Authorisation for the continued use of OPEs, the profit loss that Siemens Healthineers would experience would be very high. Importantly, customers would not be prepared to wait for years for reformulated IVD products to become available. A long period of downtime would strongly incentivise downstream users to move from Siemens Healthineers' products. Once investments into third-party analysers take place, customers could not revert back for many years;

- Reformulation of OPE-containing IVD products would also generate additional regulatory activities. The reformulated products would need to be re-registered under the many jurisdictions where they are marketed. There are about 80 countries with re-registration requirements and submission requirements to each country vary. Siemens Healthineers estimates that re-registrations would generally be required in ca. 50 countries. The review time in the different countries vary between a few months to three-and-a-half years, with China taking the longest (42 months). Re-registration activities would have to be performed at multiple Siemens Healthineers' sites, both in the EEA and in the USA. The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market;

- The continued and ultimately declining use of Triton™ X-100/Triton™ X-405 is envisaged to result in modest releases of 4-tert-OP to the environment; in total [redacted] (range: 100-500) kg are estimated (in a worst case) to be released to the UK environment across both Applied for Uses over the period 2021-2025 for Use #2 and 2021 to 33 for Use #1. The socio-economic benefits from the continued use of OPEs are significant. The economic benefits per kg of 4-tert-OP released were presented above, excluding the benefits in terms of patient diagnoses and delivery of care outcomes.

  These benefits can best be reflected in terms of the ratio of diagnostic tests that could continue to be delivered under Use #1 and Use #2 per milligram of 4-tert-OP released. These are related to **30.7** (range: 10-50) **million tests** under Use #1 representing a ratio of [redacted] (0,1 – 5 mg) per test, and [redacted] (range: 10-50) **million tests** under Use #2 and a ratio of [redacted] (range: 1 - 15 mg) per test. **These figures are at best a crude indicator of the potential benefits for UK patients' health associated with the continued use of OPEs.**

2 Aims and Scope of the Analysis

The following document is based on the authorisation applications of Siemens Healthcare Diagnostics Products GmbH (ID 0154-04 and 0154-05) which have Opinions from the European Chemicals Agency's (ECHA) Risk Assessment and Socio-Economic Analysis Committees, but are still awaiting a EU-Commission decision (status: June 2022). The aim and purpose is to apply for and substantiate an authorisation in the territory of the United Kingdom (UK) for the respective substances 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) for use in diagnostic end-uses under the REACH etc. (Amendment etc.) (EU Exit) Regulations 2019[1]. Basic explanations for the use of the substances are identical to the information submitted to ECHA. The public version of the AfA is available on ECHA's website.

The purpose of this document is to set out arguments for the continued use of OPEs in the Applied for Uses for the UK alone. As a result, figures are revised so as to demonstrate the residual risk for the UK alone. Furthermore, adjustments regarding the products used are also presented. Only products marketed in the territory of the UK are included in this application. In addition, the Analysis of Alternatives has been updated for the UK situation, also taking into account the substitution efforts that have already taken place, as well as those that have come about through new developments that involve 4-tert-OPnEO (e.g. tests developed at short notice for the detection of SARS-CoV-2).

2.1 General structure of supply chain and coverage of downstream users with the authorisation

Siemens Healthcare Diagnostics Products GmbH (hereinafter referred to as Siemens Marburg) is part of the globally operating holding Siemens Healthineers AG and is a legal entity which also encompasses the Siemens Healthineers European Distribution Centre (EDC) in Duisburg, Germany. The EDC distributes annually more than [redacted] in-vitro diagnostic (IVD) products (kit reagents and wash solutions), many of which contain either 4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol (trade name **Triton™ X-100**[2]), or (Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy- (trade name **Triton™ X-405**[3]) in typically low concentrations to [redacted] (range: 100-500) customers in the UK. These two substances fall within the group of ethoxylates of 4-tert-OPnEO and the present AfA covers the downstream use of these IVD products in the UK, namely:

[1] UK Statutory Instrument 2019 No. 758.

[2] 4-tert-OPnEO with an average of 9.5 ethylene oxide units (9 or 10) which is sold under the trade name Triton™ X-100 (4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol, CAS No. 9002-93-1 and CAS No. 9036-19-5)

[3] 4-tert-OPnEO with an average of 35 ethylene oxide units which is sold under the trade name Triton™ X-405 ((Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-, CAS No. 9081-99-6)

- **Use #1**: Use of IVD kit reagents on diagnostic analyser systems (#C (range: 50-500) IVD products), and
- **Use #2**: Use of IVD kit wash solutions on diagnostic analyser systems (#C (range: 1-10) IVD products).

The "Applied for Use" involves the application of Triton™ X-100 as a cleaning agent (detergent) and stabiliser in both Applied for Uses. Triton™ X-405 is also used as a cleaning agent (detergent) and stabiliser in Use #1 only. These IVD products are used by hospitals, commercial laboratories and research centres on several Siemens Healthineers and third-party analysers to perform vital diagnoses of specific diseases and conditions in patient samples.

Siemens Healthcare Diagnostics Products GmbH is acting on behalf of the UK (downstream) users and is requesting an Authorisation in the UK for the continued use of OPEs which will allow the continued use of the aforementioned # D (range: 50-500) IVD products in Use #1 and another #D (range 1-20) in Use #2 while efforts for phasing out the use of OPEs continue. Siemens Healthcare Diagnostics Products GmbH is represented by an Only Representative (OR) for the purpose of applying for authorisation. The OR responsible is Siemens Healthcare Diagnostics Products Ltd. located in Wales (see Figure 2-1).

Figure 2-1 Supply chain structure relevant for the AfA

The legal applicant, Siemens Healthcare Diagnostics Products Ltd. (Siemens Llanberis) on behalf of Siemens Healthcare Diagnostics Products GmbH (Siemens Marburg), wishes to continue to supply IVD kits and associated wash solutions that rely on the use of OPEs to the UK healthcare market beyond the Sunset Date, while work is underway to re-design or phase-out current products containing OPE at a concentration of 0.1% or above. The IVD products that fall within the scope of this AoA-SEA document are manufactured either by Siemens Marburg covered by EU-REACH authorisations that are awaiting a final EU Commission decision, but which have Opinions recommending 12 years for both Use #1 and Use #2, or which are manufactured at US-based sites of Siemens Healthineers or by Original Equipment Manufacturers (OEMs).

Table 2-1 summarises the numbers of relevant products that are imported to the UK. In total #D (range: 50-500) IVD products fall within the scope of the two Applied for Uses for UK REACH. This

compares to the #D (range: 50-500) products that were the scope of the original EU REACH applications and were recommended subsequently for authorisation for further use by RAC and SEAC. In this respect, it should be noted that any of the products in the original application which have not yet been reformulated (ca. #C,D) could potentially be ordered by a UK customer in the future before they are phased out, although only the #C,D (range 50-500) under Use #1 and #C,D (range 1-20) under Use #2 identified in the table have had any orders from UK customers in the last 3 years

Furthermore, the table shows the tonnages imported to the UK for Use #1 and #2 (reference year = 2021). The UK tonnage of ADVIA CC solutions (Use #2) is currently about #A (range: 5% - 20%) of the overall tonnage imported/used in the EEA as presented in the original application submitted to ECHA. Table 2-1 also breaks down the above numbers per business line.

Table 2-1: Overview of relevant IVD products within the scope of Applied for Uses #1 and #2 with indication of reformulation plans under the Siemens Healthineers REACH Response Plan

Applied for Use	Origin	Total No. products	Group	Volume [kg per use 2021]
Use #1	EDC	#D		#A
Use #2	EDC			#A

The aforementioned products are used on numerous analyser systems within the UK, including a few analysers manufactured by third-parties, as shown in **Table 2-2**. Note that these are a subset of the analysers that are relevant to the Authorisations granted under EU REACH.

Table 2-2: Analysers/systems of relevance to the Applied for Uses #1 and #2

#	Analyser/system
Analysers relevant to Marburg-made IVD products	
	(Use#1 reagents)
	#D Table (Use#1 reagents)
	(Use#1 reagents)
	(Use#1 reagents)
	(Use#1 reagents)
Analysers relevant to US/OEM-made products	
	(Use#1 reagents)
	(Use#1 reagents)
	(Use#1 reagents)
	(Use#1 reagents)
	(Use#1 reagents)
	(Use#2 washes only)
	(Use#1 reagents)

Table 2-2: Analysers/systems of relevance to the Applied for Uses #1 and #2	
#	Analyser/system
Analysers relevant to Marburg-made IVD products	
[redacted]	[redacted] (Use#1 reagents)

The aim of this Application for Authorisation (AfA) is to allow the continued use of OPEs in the form of OPE-containing IVD kit reagents and IVD wash solutions by the customers of Siemens Healthineers (i.e. customers who receive IVD products from the EDC that falls under the Siemens Marburg legal entity) beyond the UK REACH Latest Application date. The Authorisation of the continued use of OPE is requested while work is underway to re-design or phase out current products and processes where OPEs are used.

This combined AoA and SEA document aims to discuss and demonstrate the following:

- The technical and economic feasibility, availability, health and safety challenges in identifying an acceptable alternative reagent or technology, which would maintain the functionality and reliability of the affected IVD kits and wash solutions and would be approved by the relevant IVD safety authorities across the globe;

- The technical and economic feasibility and availability of alternatives for downstream users in the healthcare sector;

- The R&D that Siemens Marburg and its parent company Siemens Healthineers AG have undertaken and are planning to undertake towards the identification of a feasible and suitable alternative for OPEs for their Downstream Users;

- The socio-economic impacts that would arise for Siemens Healthineers, users of the relevant IVD products, and, crucially, patients and healthcare systems in the UK, if the applicant was not granted an Authorisation for the continued use of the impacted kits/wash solutions with an appropriately long review period; and

- The overall balance of the benefits of the continued use of OPEs and risks to the environment from the endocrine effects of 4-tert-OP into which OPEs may break down in the environment.

This AfA stands in direct relation to a set of authorisations that are about to be granted to Siemens Marburg for formulation uses and a range of subsequent different DU uses of OPEs also in the EEA. Originally, it was planned to cover the UK-DU within the framework of these AfAs, which was no longer possible due to the UK's withdrawal from the EU and which is why this application is being submitted in the UK in order to be able to guarantee security of supply for these DU within the framework of the new legislation.

3 Applied for Use Scenario

3.1 Analysis of substance function

3.1.1 The substances

The OPEs that are of relevance to the Applied for Uses and authorisation under UK REACH are shown in Table 3-1.

Table 3-1: OPE substances of relevance to this AfA (Use #1 and #2)

#	Common trade name	Chemical name	Degree of ethoxylation (EO units)
1	Triton™ X-100	(4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol	9.5 (9 or 10)
2	Triton™ X-405, used on site as a 70% solution	Oxirane, 2-methyl-, polymer with oxirane, bis(2-oxiranylmethyl) ether	35 (average)

A third substance (Triton™ X-705, CAS No. 9081-99-6) was considered in the EU REACH application, even though its use in the EU would cease before the Sunset Date.

3.1.2 IVD kits reagents and IVD wash solutions

IVD kits

In-Vitro Diagnostic (IVD) Kits are core to modern medicine, performing qualitative and quantitative tests to diagnose a broad range of diseases and health conditions. They are also used to detect genetic mutations or the presence of certain chemicals in patient samples.

For the UK market, over #C,D (range: 50-250) Siemens Healthineers IVD products are of relevance, with this representing #C,D (range: 5-20) different product lines on which the kits are used. One platform normally includes a range of analysers which perform tests within the above fields. For example, the #D platform is an Immunoassay technology, performing tests on the following range of analysers – #D . **Table 2-2** provided an overview of the impacted platform portfolio which identifies #D (range: 10-50) separate models as being impacted (this does not include third-party analysers).

Further details on the typical contents of an IVD kit can be seen in the examples of the relevant products which are shown in **Figure 3–1**. Both of the above uses take place on automated analyser systems, see example in **Figure 3–2**, and a range of different analyser system platforms are associated with these uses (see for the full list).

Figure 3–1: IVD kit (left) and IVD wash solution (right) examples

#D

Figure 3–2: IVD analyser Example – System for use in

IVD kit reagents

The function of an IVD kit reagent is to perform a chemical or biological reaction in patient samples (e.g. blood, urine) that detect, identify and quantify a number of specific molecules, and ultimately ensure an accurate diagnosis of diseases and health conditions.

In REACH terminology, an IVD reagent is a formulated mixture that contains a number of chemicals that enable a certain function when used in an assay. Key facts about IVD kit reagents are:

- They are typically supplied in low volumes (in reagents manufactured by Siemens Healthineers volumes are typically <150ml);
- They typically have low concentrations of OPE (in reagents manufactured by Siemens Healthineers the average is ca. # B % (range: 0.1-1);

- An IVD kit may contain just one reagent or several; the number is normally dependent on the number of steps needed to achieve the biochemical reaction;

- In a case where there are several reagents in one IVD kit, their interaction is key to the diagnostic test, one cannot function without the other; and

- Individual IVD kit reagents can either be bought as an IVD kit that contains all reagents needed or can be bought individually, for example, if a single reagent within a kit needs to be replenished. The number of different reagents in the IVD kit can vary. If an IVD Kit contains OPE, in some cases it will be present in only one of the reagents in that kit, in other cases it could be in multiple reagents contained within that kit.

It is important to note that every IVD kit has a certain number of assays, i.e. tests for the specific disease or condition, that can be performed using one kit. For example, the [redacted] can perform 7,500 (of the same) tests with one kit. Many IVD kits offer up hundreds or even thousands of tests within one kit.

Each IVD kit and the included reagents are specific for one particular parameter, e.g. the concentration of a molecule in a body liquid or the ratio of two molecules. The biological molecules that are detected are an indicator for pathogenic changes in the patient. In some cases, these molecules are induced by a pathogen, e.g. antibodies that are produced as a reaction to a virus infection. In other cases, the molecules are always present in in the organism (e.g. triglycerides, cholesterol), but their level is increased or decreased or even the ratio between two molecules changes and this is an indicator for a certain disease pattern. Such molecules are therefore also called “target molecules” of an IVD kit. An IVD kit does not measure the molecules in a direct way, but it facilitates a reaction with another biological molecule, e.g. a receptor protein for such a target molecule. The target molecule and the receptor are highly specific to each other and follow a lock and key principle.

The biological, and therefore highly variable nature of these parameters from one patient sample to another, requires the development of highly specific, adaptable and sensitive test reagents and optimised test protocols. Validity and reproducibility are ensured by the extensively tested, verified and registered IVD kit design combined with the design of the IVD analyser systems; thus, ensuring that patients receive accurate results as quickly as is possible.

3.1.3 Use #1: Use of an IVD kit on an analyser system

Modern analysers can be used to detect a range of diagnostic parameters (e.g. the level of a physiological molecule, an antibody or a pathogen) when used with a specific IVD kit. Each analyser system has a specific assay/test menu (see the original EU AfA for further details).

To perform an assay for a specific disease or condition, the IVD customer is essentially running a ‘ready to use’ IVD kit on a compatible analyser system. While some IVD kit reagents are concentrates and have to be pre-diluted before they can be used, no other manual steps are required apart from subjecting the sample to the test. Following this, a specific protocol is followed, the other IVD kit reagents are added to the sample and the detection occurs. Many analysers can handle several assays in a row, so an additional core functionality for the application of IVD kits is the automated sample processing and unique identification (e.g. by a bar code system) and

documentation of results. In some cases, different analysers are also connected with each other to measure a broad range of parameters in one sample – each by the application of a different IVD kit.

IVD kit operations are performed by trained healthcare staff. Siemens Healthineers provide training courses for workers that include handling of IVD kits and the operation of the analyser systems, often performed at the point of work at customer sites. Courses also include training on the maintenance of the instrument and the disposal of consumables (the kit components and the patient samples).

3.1.4 Use #2: Use of IVD wash solutions

IVD wash solutions are not normally provided as part of an IVD kit, but as a separate product. Each wash solution design is specific to the analyser system it is used on. IVD wash solutions are used with every IVD kit on an analyser system to clean and flush the internal parts which have come into contact with the IVD kit reagents and/or patient sample as part of the liquid-handling operation.

Each analyser system must be cleaned during and between each assay run to ensure there is no risk of contamination from one assay to another. An IVD wash solution is specifically designed to be compatible with all of the IVD kits run on that analyser system, regardless of whether the IVD kit itself contains OPE or not. Their technical function is to maintain a clean status between single measurements on the analyser system, which is vital for the accuracy of testing as any impurities carried over from one sample or reagent to another can affect the diagnostic result.

Key facts about IVD wash solutions:

- Each one is specific to an analyser system;
- They are used with every IVD kit on that analyser system, and must be compatible with each IVD kit, providing no interference with any kit's function;
- They are typically supplied in plastic bottles and in larger volumes than IVD reagents, up to 2000 ml;
- They are typically bought in a concentrated form and then diluted at the customer site; and
- Following this dilution step, the wash solution is normally placed on or by the machine and is automatically pumped into the relevant parts of the analyser.

3.1.5 Role of OPEs in IVD kit reagents and wash solutions

Within the entire Siemens Healthineers portfolio, OPEs were previously used in over #D IVD products used across #D different platforms on over #D different analyser models. Due to extensive work on Substitution projects over the last 5 years, the number of products containing OPE has reduced from 250 to 190, and as noted above, of these #D (range: 50- 500) products are relevant to the UK.

As previously described, an IVD kit is designed to detect molecules that are specific indicators for a disease or condition. Detection molecules in IVD kit reagents form complexes with target molecules in patient samples, causing a detectable reaction which thus indicates the specific disease or condition for which that IVD Kit has been specifically designed. An IVD kit is optimised to ensure a high specificity and a high sensitivity of the diagnosis:

- **Specificity** of an IVD kit refers to its potential to detect a certain protein with high accuracy (i.e. the detection molecule only binds to a particular type of target molecule); and

- **Sensitivity** is the degree to which an IVD Kit detects the target molecule.

OPEs are core to ensuring that this specificity and sensitivity level is maintained throughout the IVD kit's life-cycle prior to expiration of the relevant shelf-life, i.e. during all production steps, when in transport, storage at the distribution centre and customer site, and in the final application of the IVD kit on the analyser system.

OPEs are not always present in every reagent within an IVD kit – in the majority of the relevant IVD kits the OPE is present in the reagent which contains the detection molecule, while there are some cases where they are present in the calibrator reagent.

The functions that OPEs perform in IVD kits, and which ensure the specificity and sensitivity of the assay, include the following:

- To prevent 'non-specific binding' during an assay, i.e. binding of molecules which are not specific to the assay and therefore can interfere with the accuracy of the result. It is vital that the role of OPE in preventing 'non-specific binding' is maintained throughout the lifecycle of the IVD kit, from the point of production to its use at the customer site. Thus, OPE ensures the stability of the reactive components over the long shelf-life of the IVD kit; and
- To keep the reactive ingredients of the reagents active and dissolved. The high range of IVD kits reflects a high variety of target molecules that are a core part of each individual test (and in turn the high variety of detection molecules).

With respect to the first bullet, a long shelf-life is required for a variety of reasons:

- IVD kit production is performed batch-wise. It can be that a particular product is not produced at all for a certain period of time, which would be the case if there are sufficient amounts of the product still in stock;
- IVD kits distributed by the European Distribution Centre come from as far as Japan and the USA, therefore transport time must be taken into consideration; and
- The IVD kit may not be used directly upon arrival at the customer's site, only when those specific tests are ordered by the healthcare provider. In some cases, hospitals will store IVD kits to be able to verify a particular diagnosis when there is an acute suspicion a patient has a certain disease. As it may be unpredictable when this will take place, sufficiently long shelf-life has to be ensured. Shorter times would potentially lead to a situation where end-users would dispose of unused kits due to uncertainties over their accuracy.

3.1.6 Technical feasibility criteria

The technical feasibility of substitution is contingent upon:

- Retaining the functionality of active components (e.g. antibodies, enzymes or other functional proteins); and
- Avoiding unspecific interactions (protein-protein, protein-membrane, protein-surface e.g. surfaces in analysers, vials, etc.).

The OPEs mediate these effects because their molecular structure allows important physicochemical properties to materialise. These are:

- **Nonionic surfactants**, no positive or negative charges;

- **Hydrophilicity (water solubility)**: blood and other body liquids are biological, therefore aqueous (water is the solvent). As a consequence of this, the IVD kit reagents are aqueous solutions as well. OPEs possess an ethoxylate group which allows them to be soluble in water;

- **Hydrophobicity (oil solubility)**: although the specimens are in an aqueous solution, cell membrane proteins are less soluble in water and are associated with less water-soluble components in the specimens (such as e.g. cell membranes, fatty tissue – this may also apply to proteins that are involved in the IVD kits or unspecific non-target protein that is present in a sample). OPEs have a carbon chain that can interact with these components. As such, OPEs can keep these less soluble components in the solution and available for processing. The length of the carbon chain of OPEs varies depending on the degree of ethoxylation grade. The representative chain lengths within the scope of this AfA has an average chain length of 9.5 (Triton™ X-100), 35 (Triton™ X-405) and 55 (Triton™ X-705) respectively;

- **Hydrophile-Lipophile Balance (HLB)**: the function to serve as a detergent is provided at HLB values between 13 – 15. Stronger solubiliser character is provided by substances with a HLB between 15 and 18. For instance, if a surfactant has an HLB equal to 1, it is considered highly oil soluble, while a surfactant with an HLB of 15 is considered to be water soluble. The HLB number is also a measure of the percent ethoxylation (EO) of the respective surfactant. Hydrophilic surfactants are water-soluble and are used for solubilisation, detergency, and for products that will dilute readily with water. As IVD kits are based on the functionality of biological molecules and these are usually active in aqueous solution, this property is relevant for the selection of potential alternatives. The HLB of OPE increases with the number of EO units bound to the 4-tert-octylphenole. While Triton™ X-100 (9.5 EO units) has an HLB of 13.4, Triton™ X-405 (35 EO units) has an HLB of 17.6 and Triton™ X-705 (55 EO units) has an HLB of 18.4. A similar HLB in this regard could indicate if an alternative surfactant might qualify as a substitute of the specific OPE variant used in an IVD kit reagent, a washing solution for instruments or a solution used as processing agent at Siemens sites or Downstream User sites that are intended to be covered by this AfA;

- **Turbidity**: for the application of OPEs it is very important that the reagents are clear (or at least translucent), because of the photometric quantification techniques. This is only the case for HLB values above at least 10;

- **Degree of ethoxylation**: the performance of a nonionic surfactant is related to the hydrophilic portion of the molecule. The ethoxylation (EO) portion of the surfactant is the water-soluble component of the compound. The greater the EO content, the higher the water solubility of the surfactant. In some formulations, more than one nonionic surfactant may be included. For instance, in detergent applications where dirt and oil have to be removed, a surfactant with 1-3 moles EO will remove oils in substrates, while a surfactant with 7-12 moles EO will aid in the removal of dirt and particulate matter;

- **Critical micelle concentration**: a micelle is an aggregated unit composed of a number of molecules of a surface-active material. Micelles solubilise dirt and oils by lifting these debris off the surface and dispersing them into solution. Micelle formation enables emulsification, solubilisation, and dispersion of otherwise non-compatible materials. Critical micelle concentration (CMC) is the surfactant concentration at which an appreciable number of micelles are formed and thus remove particles. CMC is a measure of surfactant efficiency. A lower CMC indicates less surfactant is needed to saturate interfaces and form micelles. Typical CMC values are less than 1% by weight (e.g. Triton™ X-100 has a CMC of 0.0189% or 189 ppm, Triton™ X-405 of 2,442 ppm and Triton™ X-705 of 3,585 ppm). CMC values provide a valuable guideline for comparing surfactant detergency. Other formulation components and temperature may affect micelle formation;

- **Cloud point**: the cloud point of a nonionic surfactant is the temperature above which an aqueous solution of a water-soluble surfactant becomes cloudy. Cloud points are a characteristic of nonionic surfactants and wetting, cleaning and foaming characteristics can be different above and below the cloud point. Generally, nonionic surfactants produce optimal cleaning efficacy when used near or below their cloud point. Low-foam nonionic surfactants should be used at temperatures slightly above their cloud point. Finished products stored at temperatures significantly higher than the surfactant's cloud point may result in phase separation and instability. The presence of other components in a formulation can depress or increase the cloud point of cleaning solutions. Cloud points of Triton™ X-100 under these conditions is 66 °C, of Triton™ X-405 and Triton™ X 705 >100 °C. A cloud point should, as a consequence, be well above ambient temperatures in the countries the IVD kits are shipped to. Under extreme conditions like intense sun and road transport temperatures could rise up to 50°C.

The above criteria are mainly relevant in regard to the substitution of OPEs when reformulating an IVD kit reagent or a wash solution. An end-user may however seek an alternative to OPE in an alternative diagnostic technology. Technical criteria to consider when assessing alternative technology are:

- **Access to alternative technologies without the need to use OPEs**: alternative technologies without OPEs, if available, would have to be identified and then their suitability evaluated. A core question would be the diagnostic range that could be covered by an alternative technology, i.e. whether it would meet the range required by the individual customer;

- **Timeframe that must be met for a diagnostic result**: some diagnostic results need to be generated in a very short time; while in some cases this is as long as a few days, for emergency care a 1-hour turnaround may be required for example. This timeframe consideration is made from a patient perspective. In some cases, a quick test result is needed to be able to provide an acute treatment quickly e.g. in the case of point of care (POC) products that are typically used for acute diagnostics such as cardiac care. For some conditions, it may be acceptable to wait for the test results, e.g. blood is taken and then tested and results are only needed after a few days because the patient is not presenting symptoms for emergency care.

  Other timeframe aspects are linked to the stability of the sample. Two factors can influence this aspect: the first one is the stability of the sample with regard to the stability of the diagnostic

parameter. For some diagnostic parameters the concentration may change when a sample is stored over time. In such cases, long periods until the sample is measured would be unacceptable because results would be affected by storage, leading to inaccurate results.

Another factor that needs to be considered is the overall time a sample can be stored. In the case of blood from blood donations, the blood has to be tested in a very short time (a few hours) and then either be processed in the production of further products, stored for use on patients or used. Extended testing times could lead to a situation where the blood degenerates and cannot be used anymore.

- **Practicalities of implementing an alternative technology**: this can depend on:
  - *Availability of same range of tests*: any alternative system would need to cover the full range of tests that the end-user currently utilises within the one system. While the typical assays offered on one immunoassay system are generally offered on another, there can be tests which are unique to certain systems.
  - *Sufficient space to introduce an additional analyser platform*: any new analyser system or range of systems would need to fit within the current laboratory space. This is often a severe limitation particularly in older buildings. As per the above bullet, this could be a particular problem if additional analyser systems are required to cover the full range of tests.
  - *Availability of trained staff to perform the alternative technology*: when new analysers are introduced, the existing staff needs to be trained to be able to apply this technology. In the best case, the alternative technology is another analyser that requires similar handling to the existing analyser technology. Then some time is needed to train the staff to operate this analyser. In case the new analyser is being added to an existing one potentially a slightly increased staff number is needed (at least if the old analyser can still be operated and the systems are operated side by side). In case the technology needs far more manual handling, more staff would be needed to perform the same number of diagnostic tests.

Beyond technical feasibility issues, the budget available for investing in new technologies will play a significant role. IVD diagnostic technologies are relatively cost intensive investments for health care institutions and investing in new analyser systems when considering the capital costs and resources required across a 6-24 month timeframe would be a significant investment. The decision to perform such testing needs to be cost effective. Many institutions are either public bodies (e.g. the hospitals in some counties) or private companies (test service providers but also hospitals). In the first case the costs of buying an analyser and it operating costs would need to be covered by budgets provided by public funding. In the second case, the end-user would need to ensure that the operation of a new analyser would not have an impact on profitability. These challenges are this are discussed further in Section 4.

3.2 Market and business trends including the use of the substance

3.2.1 Introduction

The Siemens Healthineers analysers and IVD kit reagents of relevance to this UK REACH Authorisation have linkages to:

- Siemens Marburg's use of OPEs and the authorisation of the same uses as covered by this application (Use #1 and Use #2) under EU REACH; and

- IVD products are manufactured not only in Marburg, Germany by Siemens, but also by Siemens Healthineers in the USA, as well as OEM kits which are collectively distributed by EDC in Duisburg to UK and EEA-based customers.

3.2.2 Annual tonnage of OPE used per Applied for Use

In 2021, the total volume of OPE contained in the Use #1 and Use #2 products placed on the UK market equated to #A (range: 100 – 500 kg). Per use, the figures for 2021 and as projected for 2022 are:

- Use #1: #A kg (range: 5 – 50 kg) for 2022 declining until use is phased out in **2032**;
- Use #2: #A kg (range: 25 – 500 kg) for 2022, declining until use is phased out in **2025**.

The projected change in consumption over the applied for use period is given in Figure 3-1 and 3-2 below, for Uses #1 and #2 respectively.

Figure 3-3: Projected change in consumption of OPEs in the UK – Use #1

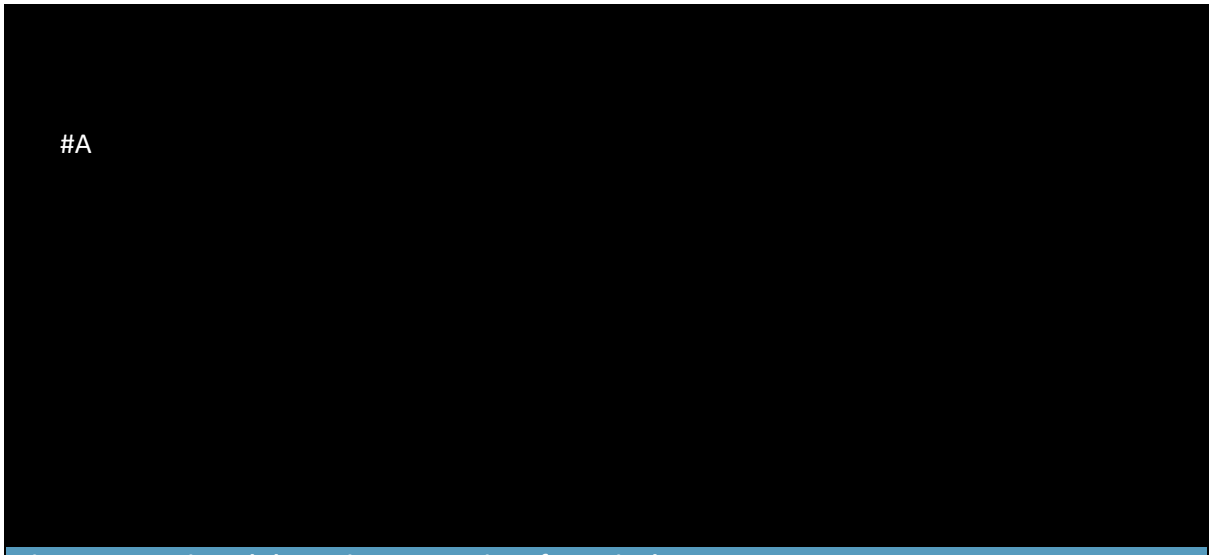


Figure 3-4: Projected change in consumption of OPEs in the UK – Use #2

3.2.3 Use #1 - IVD Kit Reagents

Within the UK, at the start of 2022, there were approximately 150 customers (range: 100 - 500) for the IVD kit reagents falling under Use #1.

In 2021, roughly #D (range: 20,000 – 50,000) IVD kits falling under Use #1 were sold in the UK. Each of these kits will support from between 50 – 500 tests. Assuming a minimum of 100 tests per kit means that sales in 2021 enabled over #C (range: 2.0 – 5.0) million tests to be carried out, assisting in the diagnoses of patient illnesses.

Of the original #D (range: 100 -1,000) products that fell under the scope of the EU REACH Authorisation, this was reduced to #D (range: 100 -1,000) via ongoing Substitution work and #D (range: 75 - 200) of these are currently sold in the UK. #D relate to Use #2, with the remainder falling under Use #1. The significant reduction in the number of products is due to the successful re-design and substitution of circa 90 (at time of writing) of the original products and hence their withdrawal from the UK market. In addition to the kits manufactured at Siemens Marburg are IVD kit products manufactured by Siemens Healthineers in the USA. Further details on the various product lines falling under Use #1 are provided in Table 2-1 and the Substitution Plan (and are available from the original AfA submitted under EU REACH - see Tables 3.4, 3.5 and 3.6). This includes information on those IVD kits that are manufactured by Siemens Healthineers in the USA and those that are manufactured by other original equipment manufacturers (OEMs) and are sold to Siemens for further formulation. Due to the COVID pandemic, additional tests for COVID were also developed where it was necessary to use OPE due to the emergency timeline, and which are now also part of the Substitution Plan.

Planned phase out of OPE and projected consumption of Triton™ X-100 and Triton™ X-405 over the requested review period

Under its current EU REACH authorisation, Siemens Marburg has undertaken and is continuing a number of Design Change projects through which #D kit reagents and #D kit

reagents will become OPE-free. Development work and timing is already near completion for the reformulation of the [redacted] #D IVD wash solution that is manufactured in Marburg and is relevant to the new [redacted] #D System. Similarly, under its EU REACH authorisation, [redacted] #D (OEM) is working on reformulation of the [redacted] #D IVD kit reagents it supplies to Siemens Healthineers (see Substitution Plan).

Siemens Healthineers in the USA is investing significant time and resources in reformulating reagents that contain OPE in the [redacted] #D and [redacted] #D product lines which are in the process of being replaced by the [redacted] #D analysers. [redacted] #D IVD kit reagents are aimed to become OPE-free by the Sunset Date, but the reformulation of the numerous [redacted] #D IVD kit reagents means that substitution of OPEs in them is now expected to take until 2032 (see Substitution Plan).

For other product lines ([redacted] #D) phase-out efforts will be completed during the requested review period (by mid-2028), while for others ([redacted] #D) as the lines are coming to retirement or are part of the [redacted] #D, G replacement programme, relevant IVD kits will be left to reach their end of life with use ceasing by 2032.

It is important to note that substitution/reformulation will happen on a 'per product' basis and the success of substituting an alternative in one product will not necessarily lead to that same substance being an appropriate substitute in any of the others, the properties which make OPE effective in one reagent may be different to the properties which make it effective in another. The reformulation process is a 'trial and error' per product process, with each project taking approximately 12-18 months to complete.

By substance, consumption of Triton™ X-405 will become very low by 2031. Consumption of Triton™ X-100 by customers is influenced by both OPE phase out efforts and projected market demand. Due to the increase in the use of [redacted] #D, G IVD kits, consumption of the substance will decline more slowly until completely phased out by the end of2032.

3.2.4 Use #2: Use of IVD wash solutions

The annual tonnage of Triton™ X-100 used by UK-based DUs in the form of wash solutions was [redacted] kg in 2021 (range: 25 – 500 kg) expected to decrease to around [redacted] kg in 2022, as shown in **Table 3-2**. Due to the ubiquitous nature of the wash solutions, their volumes (and thus the amount of Triton™ X-100 contained therein) are much higher than those of the IVD kit reagents.

The tonnages given shown in Table 3-2 and give in Figure 3-2 relate to [redacted] #B, D original product lines. Only these [redacted] #D product lines continue to be sold in the UK. The installed UK base for the use of these wash solutions is [redacted] #D analysers (range: 50 - 200), with this including a small set of hospitals which act as "power users" that consumer higher quantities than the typical laboratory and other "mini-users".

Table 3-2: Wash solutions sold to DUs in the UK in 2021 – Only Triton™ X-100

Product Line	Product	Relevant analysers	Volume sold to EEA customers (kg)/2021
[redacted]	[redacted] #D	[redacted]	[redacted] #A

[redacted]	[redacted]	[redacted]	[redacted]
		Total Triton™ X-100 volume used by EEA DUs	**280.5**

Planned phase out of OPE and projected consumption of Triton™ X-100 over the requested review period

The [redacted] #D product line is critical as it includes the [redacted] #D (OEM) products that contain the vast majority of Triton™ X-100 that Siemens Healthineers places on the UK market, and is the only wash solution product line on the UK market. This product line [redacted] #D [redacted] will be replaced by OPE-free products in 2025. After 2025, the two products will no longer be used, thus drastically reducing the overall volume of OPEs used by Siemens Healthineers' customers in the UK. These two solutions are critical to the operation of the systems and so for all tests (which are non-OPE-containing) run on those systems.

3.2.5 Market for Siemens Healthineers IVD kits and wash solutions

Sales per year and associated profits per year for Use #1 and Use #2 are given in Table 3-4. These figures are for 2021. As can be seen from Table 3-4, the value of sales and profits per annum are both relatively low, highlighting the fact that this application for authorisation is being submitted so as to ensure that customers are able to retain access to the IVD kits and wash solutions while substitutes are developed or the solutions are phased-out, thereby minimising the impacts on hospitals, labs and other health care providers (see Section 4).

Table 3-3: Sales and profits in 2021 across both uses

Customer group	2021 out-turn figures	
	Sales	Profits
Use #1	[redacted] #C,D	[redacted]
Use #2	[redacted]	[redacted]
Use #1 & #2 total	[redacted] **(range: £1-15 million)**	[redacted] **(range: £1-15 million)**

Using these figures and assuming a constant ratio between consumption of OPEs and profits and sales to Siemens Healthineers, the present value of gross profits that Siemens Healthineers anticipates making over the requested review periods equate to around [redacted] #C,D million PV terms (range: £30-100 million, discounted at 3.5%). As can be seen from Table 3-5, the majority ([redacted] #C,D) of this relates to Use #1, despite this being the lower volume use in OPE consumption terms. This is of course also due to the fact that Use #2 will be phased out by 2025. Until these Use #2 wash solutions are replaced, however, their use is essential alongside the IVD kits for Use #1 and other OPE-free IVD kits.

Table 3-4: Net present value estimates of profits over 12 year review period based on 2021 sales and profits (2022 = year 0, @ 3.5%)							
Year	Use 1				Use 2		
	% 2021 sales and profits	Profits (undiscounted)	Discounted value		% 2021 sales and profits	Profits (undiscounted)	Discounted value
22	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
23	[redacted]	#C,D Table	[redacted]		[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]				
27	[redacted]	[redacted]	[redacted]				
28	[redacted]	[redacted]	[redacted]				
29	[redacted]	[redacted]	[redacted]				
30	[redacted]	[redacted]	[redacted]				
31	[redacted]	[redacted]	[redacted]				
32	[redacted]	[redacted]	[redacted]				
Total PV rounded			[redacted]		Total PV rounded		[redacted]
Range: £25-100 million					**Range: £100k-£5 million**		

As can be seen from the above table, the value of the sales and associated profits for the Use #2 wash solutions are low. All tests carried out on the #C,D analysers – OPE-based and OPE-free – also require the use of the Use #2 wash solutions. In 2021 it is estimated that #C,D (range: 1,000 – 10,000) #C,D kits in total were sold in the UK, with these providing (range: 10 – 20) million tests. The associated sales value to Siemens is estimated at around #C,D (range: £0.5– 2.5) million, generating profits of around #C,D (range £50,000 – 200,000) per annum, or present value profits to Siemens of around £#C,D (range: £1-5 million).

Over the requested 4 year review period for Use #2, this equates to over #C million tests (taking into account the anticipated reduction in use of the wash solutions over time) helping deliver patient diagnoses and present value. As a result, until these solutions can be replaced their continued use is essential in the ADVIA 1800/2400/XPT analysers, which are the main types of Siemens analysers in use in the UK for clinical chemistry purposes. The types of diagnostic tests run on these analysers are summarised in Table 3-6 below.

Table 3-5: Disease information relating to diagnostics carried out by OPE-containing kits reliant on OPE based wash solutions under Use #2

Diagnostic field	IVD kit name	Intended use
Clinical Chemistry		
Clinical Chemistry		# I
Clinical Chemistry		
Clinical Chemistry		
Clinical Chemistry		

Source: Siemens Healthineers Document Library

3.2.6 Other Siemens Healthineers operations in the EEA

The links between the use of IVD kits and wash solutions for DUs and the operations of Healthineers in Marburg, Germany should be noted. If use of OPEs under Applied for Uses #1 or #2 are not authorised to continue in the UK, then there will be significant impacts on Siemens Marburg which has applied for an authorisation for the continued use of OPEs under EU REACH.

3.2.7 Suppliers

In the context of Uses #1 and #2, other relevant suppliers would be those supplying the users of Siemens Healthineers' IVD kits/wash solutions with other OPE-containing products. Siemens has no information on which any meaningful analysis can be presented with regard to such other suppliers' products.

A discussion on suppliers to Siemens Healthineers' EEA and US-based operations is considered outside the scope of this analysis, although impacts may be experienced by its Marburg facility.

3.2.8 Customers

Downstream users are the operators of the analysers presented above, which are in essence global products. Over the last five years (2016-2021), Siemens Healthineers Diagnostics has shipped reagents to over #C (range: 10,000-100,000) locations in the UK and EEA (as distinct from customers, e.g. some locations may be distributors supporting multiple end-users).

Under the "Applied for Use" scenario, Siemens customers in the UK would not experience any disruptions in the supply of OPE-dependent products, and their operations can continue as usual.

Commercial laboratories that use Siemens Healthineers analysers will typically have a profit from the use of the IVD reagents/wash solutions, but many end users like hospitals, research facilities and other will have negligible profits. It has not been possible to obtain estimates of the profits that Siemens Healthineers' customers located in the UK gain from the use of OPE-containing reagents and wash solutions.

3.2.9 Employment in the "Applied for Use" Scenario

The analysers and IVD reagents/wash solutions are not produced in the UK, so there is no direct employment in the UK in their manufacture. There are ~500 jobs located in the UK linked to the Siemens' supply chain for these diagnostic products for servicing and managing sales, #E

3.3 Remaining risk of the "Applied for Use" scenario

3.3.1 Emission sources and existing risk management measures

Environmental classification

The environmental classifications for 4-tert-OP, a degradation product of OPE, are given in the following table.

Table 3-6: Environmental classification of 4-tert-OP		
Hazard class	**Hazard category**	**Hazard statement**
Hazards to the aquatic environment (acute/short term)	Aquatic Acute 1	H400 Very toxic to aquatic life
Hazards to the aquatic environment (chronic/long term)	Aquatic Acute 1	H410 Very toxic to aquatic life with long lasting effects

Emission sources

Triton™ X-100 and Triton™ X-405 are present in IVD kit reagents and IVD wash solutions that are used by numerous DUs across the EEA.

In most cases, the consumed reagents and wash solutions are flushed to the drain and end up in the communal wastewater. This applies also to OPE-containing solutions and thus the assessment in the CSR considers 100% of the used OPEs are discharged to wastewater. Only a few customers collect the reagents after use and dispose it of as waste. This is especially the case where the waste solutions are contaminated with potentially infectious material. The amount not released via wastewater can, however, not be quantified.

A small proportion of the applied OPE (CSR assumption: <0.1%) adheres to solid waste like pipettes, gloves, wipes or containers, which are collected as solid laboratory waste (PROC 21) for incineration. Since this volume cannot be adequately quantified, it was not considered in the calculation of emissions to wastewater in the CSR.

As regards the application of sludge to agricultural soil, and based on Eurostat data, the CSR assumes that 53% of STP-sludge is applied to agricultural soils or compost (ECHA, 2019).

Finally, it is assumed that any disposable materials like gloves, lab coats, pipettes, one-time pipes, which may be contaminated with OPEs, is disposed of as solid waste for incineration.

The following table summarises the emissions to the environment.

Table 3-7: Summary of emission sources associated with the use of OPEs by Siemens Marburg's DUs	
Environmental compartment	**Release method**
Water	Via municipal STP discharge into local waterbodies
Soil	Sludge from municipal STP (53% of sludge is applied on agricultural soil across the EEA)
Air	There is assumed to be no release to air

3.3.2 Exposure levels

Overview of exposure assessment

In total, roughly #A (range: 1,000 – 5,000) kg of OPEs are associated with the continued use of Triton™ X-100 and Triton™ X-405 in the IVD kit reagents and wash solutions sold to UK downstream users under the "Applied for Use" Scenario. The following table summarises emission factors that have been used in the CSR for the estimation of releases of OPE/OP to the environment that are associated with Use #1 and Use #2.

Table 3-8: Key emission parameters for the estimation of environmental impacts under the "Applied for Use" Scenarios		
Emission parameter	**Use #1**	**Use #2**
% of consumed Triton™ X-100 released to water (as 4-tert-OP)	**26.5%**	**26.5%**
% of consumed Triton™ X-100 released to sludge (as 4-tert-OP)	6.5% × 53% = **3.45%**	6.5% × 53% = **3.45%**
% of consumed Triton™ X-405 released to water (as 4-tert-OP)	**9.5%**	N/A
% of consumed Triton™ X-405 released to sludge (as 4-tert-OP)	2.3% × 53% = **1.22%**	N/A
Is sludge applied to agricultural soil?	Yes	Yes

Estimated releases of 4-tert-OP under the Applied for Use" Scenarios

Use #1

The total emissions of 4-tert-OP to the environment under the "Applied for Use" Scenario for Use #1 are shown in **Table 3-9**. The combined releases to the aquatic and terrestrial environment account for a total of ca. #H, J kg (range: 10 -75) kg over 12 years.

Table 3-9: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100/Triton™ X-405 by Siemens Healthineers' customers in the EEA – Use #1			
Year	**OPE amount used (kg)**	**4-tert-OP releases to aquatic environment (kg/y)**	**4-tert-OP releases to sludge (kg/y)**
2022			
2023			
2024			
2025	#A	#H, J	
2026			
2027			
2028			
2029			
2030			
2031			
2032			
2033			
Total, 2022-2033 Range 0-200			

Use #2

The total emissions of 4-tert-OP to the environment under the "Applied for Use" Scenario for Use #2 are shown in **Table 3-10**. The combined releases to the aquatic and terrestrial environment account for a total of ca. #H, J kg (range: 100-500) kg over 4 years.

Table 3-10: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 by Siemens Healthineers' customers in the EEA – Use #2			
Year	**OPE amount used (kg) Triton™ X-100**	**4-tert-OP releases to aquatic environment (kg/y)**	**4-tert-OP releases to sludge (kg/y)**
2022	#A	#H, J	
2023			
2024			

Table 3-10: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 by Siemens Healthineers' customers in the EEA – Use #2			
Year	**OPE amount used (kg) Triton™ X-100**	**4-tert-OP releases to aquatic environment (kg/y)**	**4-tert-OP releases to sludge (kg/y)**
2025	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]
Total, 2022-2026 Range: 0-1000	[redacted]	[redacted]	[redacted]

Environmental quality standards

Table 3-11 provides the relevant EQS-values[4] of 4-tert-OP for each of the environmental domains, as presented and discussed in the CSR. The figures in the table are only provided for comparison and orientation purposes.

Table 3-11: Latest research values (as presented in the CSR)	
Environmental domain	**EQS**
Freshwater sediment	82 µg/kg dry weight
Freshwater	0.100 µg/litre
Marine water	0.010 µg/litre
Marine sediment	8.2 µg/kg dry weight
Soil	17 µg/kg dry weight

Predicted environmental concentrations

Table 3-12 provides the predicted local concentrations of 4-tert-OP in the **local and regional environment** over the requested review periods 2022-2033, as presented in the CSR. All values provided (for the year 2022) are below the respective EQS values shown in **Table 3-11**.

Table 3-12: Predicted environmental concentrations, local and regional, Uses #1 & Use #2 (2021)					
Compartment	**EQS values**	**Local PECs**			**Regional PECs Uses #1-2**
		Use #1	**Use #2**	**Combined Uses #1-2**	
Fresh water	0.0001 mg/L	**Local PEC:** [redacted]E-7 mg/L	**Local PEC:** [redacted]E-6 mg/L	**Local PEC:** [redacted]E-6 mg/L	**Regional PEC:** [redacted]E-8 mg/L
Sediment (freshwater)	0.082 mg/kg dw	**Local PEC:** [redacted]E-5 mg/kg dw	**Local PEC:** [redacted]E-3 mg/kg dw	**Local PEC:** [redacted]E-3 mg/kg dw	**Regional PEC:** [redacted]E-5 mg/kg dw
Marine water	0.00001 mg/L	**Local PEC:** [redacted]E-8 mg/L	**Local PEC:** [redacted]E-6 mg/L	**Local PEC:** [redacted]E-6 mg/L	**Regional PEC:** [redacted]E-9 mg/L
Sediment (marine water)	0.0082 mg/kg dw	**Local PEC:** [redacted]E-6 mg/kg dw	**Local PEC:** [redacted]E-4 mg/kg dw	**Local PEC:** [redacted]E-4 mg/kg dw	**Regional PEC:** [redacted]E-6 mg/kg dw
Agricultural soil	0.017 mg/kg dw	**Local PEC:** [redacted]E-6 mg/kg dw	**Local PEC:** [redacted]E-4 mg/kg dw	**Local PEC:** [redacted]E-4 mg/kg dw	**Regional PEC:** [redacted]E-8 mg/kg dw

[4] See: Directive on Environmental Quality Standards (Directive 2008/105/EC)

Post-2022 trends	Steady decline until 2032, with use ceasing in 2033	Steady decline to 2025 [redacted] #F, H Table [redacted]	Steady decline until 2025 (dominated by Use #2), with continuing decreases thereafter

Environmental 4-tert-OP concentrations calculated for the local scenarios in 2022 due to the wide dispersive Use #1 are below the EQS used as indicative values for risk characterisation. For Use #2 the calculated local PECs are higher, but are still about a factor of 3 below the EQS. However, by the end of 2025 the consumption of [redacted] # D that contain the bulk of Triton™ X-100 present in scope of Use #2 wash solutions will cease and this will cause a dramatic decrease in local PECs, as the 'power users'[5] assumed as a worst-case scenario in the CSR will no longer use these products.

On the regional scale, the calculated aquatic PECs due to all uses are factor 100 below the relevant EQS, while the PECs for sediment and soil are more than two orders of magnitude below these indicative values. Thus, adverse effects for water and sediment organisms are less probable than in the local scenario.

The estimated release and the calculation of environmental concentrations above are considered reasonable worst-case. Based on the following aspects the exposure is considered to be an overestimation rather than an underestimation:

- Residual reagents and wash solutions remaining in the vials after use of the IVD kits are disposed of as solid waste. The volume of these waste solutions cannot be quantified, but is probably in the range of 0.5-1% of all wide dispersive uses. The release figures from Uses #1 and #2 can thus be considered a (slight) overestimation;

- In some IVD kit reagents Triton™ X-405 is used, which has a lower 4-tert-OP content. The release figures for Use #1 thus represent a slight over-estimation;

- Since the daily release figures used in the CSR to calculate local PECs are based on 'power users' of [redacted] # D wash solution, the scenario considers already the local worst case of daily releases and exposure. Hospitals or service labs such as the [redacted] # C, I used in the example are usually located in urban centres. The local STP capacities and flow rates will thus be much higher than the standard figures for wide dispersive uses in the EUSES model. It is thus very unlikely, that an individual local assessment would result in higher local PECs;

[5] As explained in the CSR document, this scenario considers 'power users' with a high local tonnage (up to 100-fold compared to the EUSES default) located in an urban area. For this urban area, an STP with a higher capacity for the local STP and the receiving water is assumed (minimum 10-fold compared to the default value of 2000 m^3/day for STP and 20,000 m^3/day for the receiving surface water).

- Microorganisms present in urban and industrial STPs are probably adapted to 4-tert-OP and thus environmental degradation may happen faster than considered in the CSR calculations, thus leading to lower 4-tert-OP concentrations in all environmental compartments; and

- In modern STPs, longer retention times than considered in the calculation can be assumed and will reduce the 4-tert-OP released from STP, while the presence of 4-tert-OP in the sludge will increase. This may lead to lower 4-tert-OP concentrations in the aquatic compartment, while the 4-tert-OP concentration in agricultural soil may increase.

3.3.3 Summary

In summary, the percentage of total OPE used that is assumed to be emitted to the aquatic environment as 4-tert-OP is 26.5% of the Triton™ X-100 consumed (including small proportions of Triton™ X-405 in IVD-kits). For releases to agricultural soil in the form of 4-tert-OP bound on sludge the release factor is 6.5% for Triton™ X-100.

In 2022, consumption of OPEs for Use #1 is projected to be ca. # A kg (range: 10-50) kg while for Use #2 the projected consumption of Triton™ X-100 is ca. # A kg (range: 100-500) kg. For both uses, the consumption of OPEs will decrease thereafter.

For Use #1, PECs for all compartments in the year 2022 are below the relevant EQS and remain so throughout the requested review period (2022-2033). For Use #2, the worst-case assumptions for 2022 made in the CSR mean that environmental concentrations are a factor of 10 below the EQS values and remain at those levels until the end of # F. On the regional scale, the PECs calculated in the CSR are below the EQS by a significant margin.

In terms of releases, over the requested review periods, the releases of 4-tert-OP to the aquatic environment account for a total of ca. # H, J (range: 10-50) kg for Use #1 and # H, J (range: 100-500) kg for Use #2. The respective releases to agricultural soil as sludge are ca. # H, J (range: 10-50) kg for Use #1 and ca. 56 (range: 50-100) kg for Use #2, over the respective review periods.

Table 3-13 summarises the releases of 4-tert-OP to the aquatic environment and sludge for both Applied for Uses. Over the period 2022-2033, the total release is #H, J (range: 100-500) kg 4-tert-OP.

Table 3-13: Estimated total release of 4-tert-OP to the aquatic environment from Uses #1 and #2

Year	4-tert-OP release to aquatic environment for both Applied for Uses	4-tert-OP release to sludge for both Applied for Uses	Total 4-tert-OP release per year
2022	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]
2025	# H, J Table	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]

Table 3-13: Estimated total release of 4-tert-OP to the aquatic environment from Uses #1 and #2			
Year	4-tert-OP release to aquatic environment for both Applied for Uses	4-tert-OP release to sludge for both Applied for Uses	Total 4-tert-OP release per year
2032	[redacted]	[redacted]	[redacted]
2033	[redacted]	[redacted]	[redacted]
Total **Range: 50 – 400**	[redacted]	[redacted]	[redacted]

4 Selection of the "Non-use" scenario

4.1 Efforts made to identify alternatives

4.1.1 Research and development

Introduction

The identification and implementation of an OPE alternative, or several combined alternatives, as a substitute in an existing commercial IVD product is an intensive, technically-challenging and time-consuming task requiring strict adherence to legally-required quality management procedures – involving extensive feasibility testing, product validation, commercialisation activities and regulatory approvals granted in each country where sold.

In this section we will describe the following processes:

- **Changing the Design of an IVD Product** – The technical considerations and methodology, also the regulatory processes which must be followed in order to change the design of an IVD Product;
- **The Challenging Nature of Identifying an Alternative Substance to OPE's –** A description of the upfront technical challenge and those which can be expected to arise as part of design change;
- **Developing and Implementing a Substitution Strategy** – A description of the plan Siemens Healthineers has mobilised to phase out OPE's from its product-lines; and
- **Past and Current Research and Development** – Efforts made in recent years by Siemens Healthineers to identify OPE alternatives for use in its OPE-containing products.

It is important to note that, as previously explained in this document, Siemens Healthineers manufactures a large number of products and thus formulations containing OPE. These products are used across many different product-lines performing a variety of functions, and therefore the technical and regulatory processes and challenges can vary between Design Projects. While every design project must move through certain prescribed steps, there are some steps which will only apply in some cases; also, the technical challenges will vary between designs. As such, we present a 'typical' route below whilst also highlighting difficulties which could arise in some projects and thus affect the success and/or timeline of those projects.

Changing the Design of an IVD Product

Each product-line operated within Siemens Healthineers has a dedicated 'Product Health Team' (PHT) with representation from different functions across the business. This team assesses and verifies whether the design of a commercialised IVD Product must be changed, weighing this against other business needs and priorities. When it is agreed by the PHT that the design of a commercialised IVD Product must be changed, such as to substitute OPE's, a Design Change Project can be initiated.

When changing any aspect of an IVD product's design it is vitally important that stringent and standardised steps are followed to ensure that any changes do not affect the performance of that product. For example, it is absolutely vital that a product which offers a diagnostic test for tumour

markers must continue to detect those tumour markers within the same stated performance parameters to ensure each patient receives an accurate result, no matter what change was made. It is a legal requirement to have these procedures in place and to document that they are always followed.

The project process is stringently proceduralised, with this procedure subject to thorough audit by relevant regulatory authorities. To ensure day-to-day adherence to the procedure, there are many layers of internal approval by subject matter experts within the business, with every step documented, and which are also checked methodically through audit by regulatory authorities and as part of regulatory submissions.

The phases of a Design Change Project are shown in **Figure 4-1**, this captures the steps which are undertaken to develop a new product, and then the steps that must be taken in terms of changing a design post-commercialisation (grey box), as is the case with many of the Siemens Healthineers' OPE-containing products.

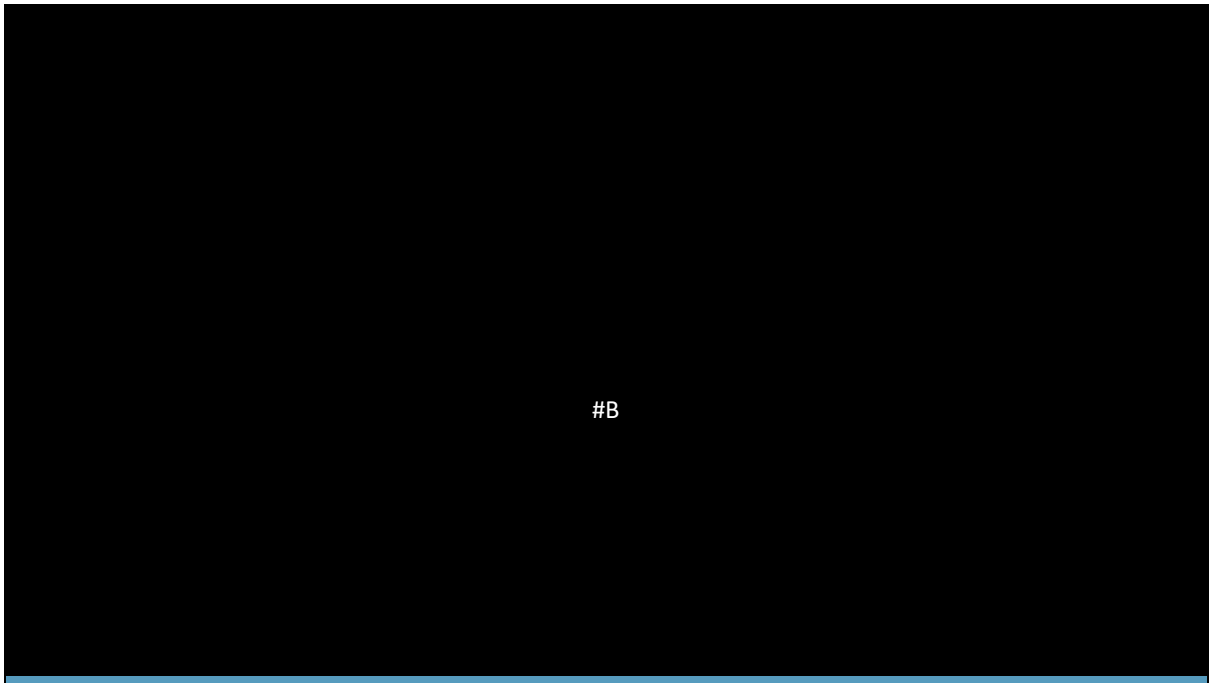


Figure 4-1: Product Design and Design Change Process Steps

It should be noted that the initial work to identify alternatives which will be tested as part of a Design Change Project is done prior to embarking on the 'Define' phase of the project (Figure 4.2). As previously noted, the efforts already made by Siemens Healthineers to identify potential alternatives are described later in this section and examples given of the Design Change projects already underway to substitute OPE's in specific projects.

Each of the activities under the four tasks,

- Problem definition and preparation of Design Change Project,
- creation of a design change Plan,
- Execution phase and

- implementation phase (manufacturing),

are specifically set out in the Siemens Healthineers extensive governing procedure for Design Change (# F) with 31 supporting documents to direct and support the responsible personnel through each task in a prescribed way which can be clearly tracked and documented. When one considers that each manufacturing site also adopts a local version to implement this global procedure, also addressing any regional or national regulatory requirements, the number of working documents significantly increases.

Each stage of a Design Change Project will typically involve resources from a range of business functions including Quality Governance, Quality Management, Marketing, Product Portfolio Management, R&D, Technical Operations, Procurement, Manufacturing and Regulatory Affairs; also, potentially Engineering, Logistics and EHS.

In the case where a fundamental design change is undertaken, such as the change of a substance used in the formulation itself (as in the case of OPE's), the Feasibility Stage of a project is key in testing the efficacy of any alternative substance. This covers the identification of alternatives and an extensive laboratory testing phase which all ends up in an evaluation and documentation in a report.

It is also important that Regulatory Assessments must be performed to determine if the planned change will need to be submitted for regulatory approval. Depending on the assay and the extent of the planned change of design, a regulatory submission will be prepared.

Generally, at Siemens Healthineers, the processing of a change project that results in a regulatory re-registration of an IVD kit includes the following steps:

1. A Change Project initiated by the central Siemens Healthineers change team;
2. An Initial Regulatory Assessment is prepared by the Regulatory Affairs (RA) function;
3. A Product Change Notification is sent to all Country RA representatives to inform them of the change and request feedback on registration impact and supporting document needs;
4. The Product Change Notification feedback is then consolidated and provided back to the central change team to incorporate requirements into project planning;
5. The RA representative reviews the change verification plans and reports and prepares and collects the requested documentation to support each country's re-registrations. The Regulatory Assessment is updated based on the verification results and the Country RA feedback; and
6. Each Country RA representative prepares the applications to be submitted to their regulatory Authority. Q&A between Country RA and Business line RA would follow as needed to generate the required submission content.

Siemens Healthineers typically allows # B months for submission preparation in each country. There are about 80 countries with re-registration requirements and submission requirements to each country vary. If there are performance changes, most countries will require a re-registration; a change in formulation may require a new 510(k) in the USA and re-registration in many countries. In 2018 the US FDA 510(k) filings fee was US$10,566 per submission. In the case of a premarket Approval (PMA) product (there are a number of these in scope of Uses #1 and #2), a PMA 180-day

supplement is required at a cost of US$48,322. If there is no performance change, some countries may still require re-registration due to an Instruction for Use (IFU) change related to composition. Importantly, all performance claims need to be verified. Siemens Healthineers estimates that re-registrations would generally be required in approximately 50 countries. This estimate is based on the fact that about 80 countries have regulatory requirements and 31 work under EU regulations (27 EU Member States and 4 EFTA Member States). The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market.

Table 4-1 gives a non-exhaustive overview on the periods it takes (on average) to get the regulatory permit. In China, a very important market, the registration of an IVD product requires 42 months, which represents the worst case; in other regions-countries, re-registration takes between 0.5 and 2 years. Given the long periods that bind significant research resources it is not possible to start the substitution activities for all products produced in Marburg at the same time.

Overall, the entire re-registration process can be expected to take up to # B, or ca. 4 years[6].

When taking into account the time for re-registration of a product, the full Design Change process can take 5-12 years, however this can alter dependent upon the particular challenges which arise in relation to each project.

Table 4-1: Worldwide IVD regulatory impact on OPE substitution timeline (non-exhaustive list of regulatory timeframes by country)

Region	Country	IVD Legislation	Estimated timeframe for a new product registration to be granted (in months, unless specified)
EU & EFTA	EU countries	IVDD (87/79/EC)/ IVDR (EU 2017/746	1-6 Timeframe for IVDR unknown
North America	USA (including Puerto Rico)	Code of Federal Regulations (21CFR.814)	Class 1 or 2, Reserved (510k): 6 - 12 Class 2 (510k): 6 - 12 Class 3 (PMA/Periodic reports): 9-12
	Canada	Canadian Medical Device Regulation SOR/98-282	Class I: N/A Class II: 1 Class III: 6 - 8 Class IV: 12
Middle East	Russia	Roszdravnadzor Resolution No 1416	12-20
	Saudi Arabia	Saudi Food & Drug Administration - National Provisions and Requirements for Medical Devices	3
	U.A.E.	Medical Device Registration Guideline (2011)	1

[6] One time constraint here is China where re-registration can take 2-3 years. In China, type testing needs to be performed in accordance with the China Product Standard or the Product Technical Requirements (PTR, 3 different reagent lots; the product must be approved in either the country of the legal manufacturer or the physical manufacturer; Report and Technical Documents for Assays; Risk Management Report; Product Summary; Clinical Trial / Study Data / Method Comparison).

Table 4-1: Worldwide IVD regulatory impact on OPE substitution timeline (non-exhaustive list of regulatory timeframes by country)			
Region	**Country**	**IVD Legislation**	**Estimated timeframe for a new product registration to be granted (in months, unless specified)**
Asia Pacific	Japan	Pharmaceuticals and Medical Devices Act	Class I: N/A Class II: 6 Class III: 6 - 24
	India	Drugs & Cosmetic Act and Rules	Notified: 9 Non-Notified: 3
	China	Administrative Measures for the Registration of In Vitro Diagnostic Reagents (CFDA Order No. 5 2014)	42
	Thailand	Medical Device Act 1988	General Medical Device: 1 - 2 Notification Medical Device: 12 Licensed Medical Device: 16
	Philippines	Administrative Order 2018-0002	9 – 12
	Australia	Therapeutic Goods Act (1989)	Class 1: 2 - 4 weeks Class 2: 4 - 6 weeks Class 3: 6 weeks - 6 months Class 4: 9 - 12 months
	Singapore	Health Products (Medical Devices) Regulations 2010	6 - 9
	Taiwan	Regulations for Governing the Management of Medical Devices	Class 1: 3 - 6 Class 2: 8 - 18 Class 3 with predicate device: 12 - 18 Class 3 new device: 18 - 24
	Vietnam	Circular 44/2014/TT-BYT and Circular 47/2010/TT-BYT	6 - 8
Latin America	Mexico	In Vitro Diagnostic Devices (IVDs): Rules 19 and 20	18
	Brazil	IVD regulation RDC 36/2015	Class I: 3 - 6 Class II: 3 - 6 Class III: 9 - 12 Class IV: 9 - 12

The Challenging Nature of Identifying an Alternative Substance to OPEs

There are some key factors to take into consideration when discussing the technical challenge faced by Siemens Healthineers in changing the design of its OPE-containing products -

- Each IVD formulation is designed to test for a different disease or condition and is therefore designed to interact with a different 'shape' molecule which is biologically variable.

  As an analogy – It is like manufacturing hundreds of different jigsaw designs, except the pieces are microscopic and there are dynamic biochemical reactions happening between the pieces and their environment which can prevent them from inter-locking and cannot always be predicted;

- An IVD product is typically a collection of raw materials and different components (the reagent formulation, a solid phase [such as a bead], controls and diluents) designed to interact with a

patient sample. Each of these interact with each other and other mixtures used on the analyser such as Wash Solutions or substrate. Therefore, any change in design must be proven not to affect the interaction with any other raw material or component, or the patient sample itself;

- For the reasons above and the different functions OPEs mediate across the impacted portfolio we know there will be no 'one size fits all' alternative – Design Change work already undertaken has also proven this (this work is described further later in this section);

- Testing must be done on a 'per formulation' basis. While the substitution strategy described later aims to group similar or high priority products in the same project, there are no short-cuts in terms of feasibility testing. Each design must be subject to its own set of feasibility testing often with a different set of OPE alternatives;

- The successful alternative cannot be known upfront. While technical feasibility criteria can be used as a guide, alternatives are primarily selected on an empirical basis and it is only through 'trial and error' testing with each identified alternative on a 'per formulation' basis that a successful alternative can be identified in the case of each IVD formulation design; and

- The impacted range of products which use OPE is significant - with # C products originally containing OPE, now reduced to 190 through substitution work. The scale of the project-work and resources required to phase out OPE's is a huge undertaking and requires skilled coordination across functions, countries and # D (range: 10-25) product-lines and extensive collaboration in terms of technological knowledge in R&D.

Each design is different and subject to biological variability

A significant technical challenge in substituting OPE's in an IVD reagent or a formulation used to manufacture an IVD Product (such as in the case of the reagents and wash formulations in scope of this AfA) is presented by the variability at the molecular level within each IVD design.

Each Siemens Healthineers platform is based on its own core technological principle or 'template', and each formulation used within that platform is unique in its biochemical function & design. This is because each formulation is biologically variable, i.e. the analyte to be detected is specific to the disease/condition it represents.

It is not possible to predict prior to testing an alternative what interaction it will have at the molecular level with the other biological and chemical components in the buffer solution and what effects, other than its intended function, it may cause and thus interfere with the final test result. See **Figure 4-4** for the description of a typical immunoassay 'Sandwich ELISA' reaction.

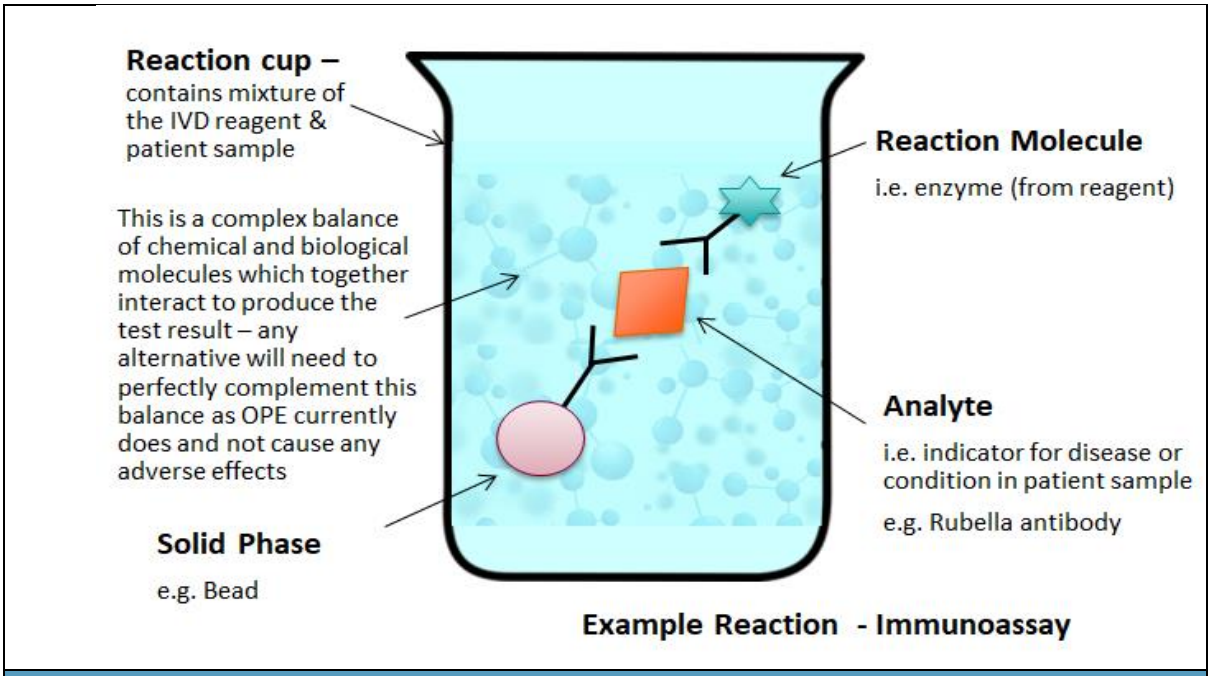


Figure 4-2: Example of the reaction in an immunoassay test
NB. When referring to many IVD products within the scope of this AfA, OPE is typically found in the IVD reagent itself

Reaction at the molecular level

To describe the reaction shown in **Figure 4-4** in more detail, each individual IVD formulation is designed to detect a different target molecule, known as an 'analyte', in a patient sample that serves as an indication for a certain disease or physiological status, e.g. an antibody. Each analyte is detected by making use of highly specific detection molecules, which are normally proteins that have a specific binding site for the analyte. Often these are antibodies, hormone receptors, or similar proteins that can bind analytes with a high specificity. The specificity of these types of molecules is based on their potential to bind to biological structures following the lock-and-key principle. This means they have a 3-dimensional protein structure that fits to a particular complementary structure on the surface of the target analyte. These complexes can then be used to quantify the target protein in the patient sample.

Maintaining the balance of the design

R&D personnel are acutely aware that changing any aspect of an IVD product's fundamental design can move the test out of balance and produce erroneous results. This is another reason for the extensive Design Change Project process, which is itself designed to ensure that a change is only implemented where continued reliable performance of the test can be fully verified.

Each IVD reagent or buffer formulation contains a different set of raw materials at specific volumes and concentrations which have been thoroughly tested and proven to interact in a perfect balance in order to detect a specific analyte, i.e. disease or condition. It is important to note that the concentration of OPE and the other constituents in each IVD reagent formulation have been specifically optimised via the extensive feasibility testing conducted during their initial product development, and are typically slightly different across the various IVD product designs. Variations

in the OPE concentration as small as 10 ppm range, i.e. ca. 0.001%, may affect the specificity and sensitivity of the test.

OPEs, when used to optimise the performance of a certain attribute of an IVD formulation, may also maintain a fine balance in regard to the optimal performance of another attribute within the same formulation. Thus, replacing OPE with another substance may move the formulation out of balance and cause inadvertent reactions which cannot be predicted.

Possible analogies which could be used to illustrate this scenario are as follows -

1. Exchanging enzymes in biological washing powder – the new enzyme cleans as effectively but inadvertently causes colour-loss

2. Two people use the same soap, both are clean but causes sensitisation in one person because of biological variability – this reaction cannot be predicted prior to effect.

As stated previously, OPEs used in scope of this AfA ensure the sensitivity and specificity of tests and in the case of the wash solutions act as a cleaning agent. If reformulation work was undertaken with these products, any alternative substance would have to be proven to fulfil these functions while not having any adverse effect on the physical and biological functions of other constituents. Performance must be proven beyond a doubt through trial and error testing in the feasibility stage, and often followed by real-time stability testing matching the shelf-life of the product, before any commercialisation activities can commence. The timelines associated with this are extensive and described elsewhere in this section.

In summary:

- Substituting OPEs with a feasible alternative may maintain the performance the OPE intended to facilitate, however, may inadvertently decrease the performance of another attribute;

- It is not possible to predict prior to testing an alternative what interaction it will have at the molecular level with the biological and chemical components involved in the reaction, and what effects, other than its intended function, it may cause and thus interfere with the test result;

- Feasibility work to identify suitable alternatives must investigate all areas of performance and involves substantial 'trial and error' testing activities to identify any potential inadvertent reactions; and

- The feasibility studies required are extensive and must demonstrate the same performance level of the overall IVD product (in terms of specificity and sensitivity).

Additional Consideration – Use #2 Wash Solutions

In regard to the technical challenge described above, an additional challenge is introduced when reformulating wash solutions. Wash solutions are used with every IVD test performed on an analyser, and therefore residues from the wash formulations can be retained on the analyser system which then interact with the chemical and biological constituents of the reagents used in the IVD formulations which perform the tests. As a result, any change in the design of an IVD Wash Solution must be tested with every single IVD product used on each analyser to demonstrate that there is no

adverse effect on each product's performance. If testing shows that any single IVD product is adversely affected then feasibility testing with another alternative must be initiated and the process repeated.

No 'one size fits all' alternative

Given the wide range of functionalities that OPEs mediate in IVD products, it is certain that there is no 'one size fits all' alternative which could be successfully substituted in every IVD Product in scope of this AfA #D, and certainly not across the wider impacted Siemens Healthineers portfolio. An adequate substitute for one functionality will often lead to poorer performance for another key functionality, as demonstrated in the alternative testing activities already conducted by Siemens Healthineers and further described in the text later in this section entitled 'Past and Current Research and Development'.

This is further demonstrated by the fact that other detergents are already in use in IVD products within the Siemens Healthineers portfolio and across the industry; this is because they have proven to be the most effective detergent substance of all those tested for the particular IVD product design they are used in. Just as OPE has proven itself to be effective in the IVD product designs in which it is currently used. Triton™ X-100 has historically been very effective in a wide range of applications, hence its use in the large number of Siemens Healthineers products. However, this detergent does not work in all IVD kits that follow the exact same test principle with regard to the test set up and detection method. Once again, this is based on the need for different target and detection molecules.

The development of an IVD product involves a high degree of empirical observations as it is not always possible to determine the substance property or a set of substance properties that are responsible for the particular function that needs to be realised. Some physico-chemical properties, such as those listed in Section 3.1, can be used as indicators that a potential alternative detergent might qualify as an alternative and that makes them a candidate for further empirical studies.

This means that 'trial and error' testing of a range of alternatives must always be performed on a 'per formulation' basis to prove the efficacy of an alternative in its intended function while not causing the adverse reaction with other molecules already described.

Technical Resource Challenge – Wider Portfolio

When taking into consideration the wider Siemens Healthineers product portfolio (including all products in scope of this AfA and the other Siemens Healthineers linked EU REACH authorisations), the technical challenge increases in scale and complexity.

As noted, each platform is based on its own core technological principle or 'template', and each formulation used within that platform is unique in its biochemical function & design. Typically, R&D personnel are allocated to and specialise in specific technologies within the business. With over # D IVD products (representing #D formulations) affected across # D platforms, the technical challenge in terms of initiating multiple Design Change Projects with only a certain availability of technical resources significantly increases.

This limitation, along with a number of other factors described in this section in terms of Design Change Project requirements and timelines, also the anticipated life-cycle of platforms and specific

products, has been taken into account when developing the Substitution Strategy for phase out of OPE's. This strategy is described in the following text.

Developing and Implementing a Substitution Strategy - The 'REACH Response Plan'

#D

. As well as the technical challenge described in the preceding text, transitioning to alternatives requires significant investment in terms of monetary spend, the time and technical resource required to complete Design Change Projects, regulatory registration requirements and other commercialisation activities, and ultimately carries the risk of affecting product performance.

As a result, in order to develop a through and appropriate substitution strategy, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a Substitution Plan.

An overview of the Siemens Healthineers Substitution Plan pertinent to the UK is shown in **Figure 4-3**. Note that this is an update and excerpt of the plan submitted as part of the Siemens Marburg AfA under EU REACH and which now only refers to the products used in the UK.

Figure 4-3: Siemens Healthineers REACH Response Plan overview

Past and current research and development

In 2012, Siemens Healthineers initiated work to establish the role of OPEs across its global portfolio and pursue the identification of potential alternatives which could be used in its IVD kit reagents and wash solutions. With the knowledge that OPEs were widely used across the global operating units and supply chains, three main work-streams were initially identified and initiated:

1. The identification and quantification of OPEs used across the global operating units and global supply chains
2. The development of a strategy to prevent the use of OPEs in any new product development
3. The identification of alternative surfactants which could be used in new product development and potentially in any future re-design of existing products.

These are further expanded below.

1) Identification and quantification of OPEs across Siemens Healthineers

The initial project to identify the uses of OPE throughout the global operating units and supply chains was significant, to not only confirm the numbers of uses and concentrations of OPE at or greater than 0.1% across a portfolio which includes thousands of saleable products, and which are often combinations of various liquid components, but also the use of OPEs in any raw materials from suppliers or OEM partners. This work took 6 months to complete, across all business-lines, and with many updates, additions and amendments made in the years following. This project ultimately identified the use of OPEs in more than # D saleable products, representing # D unique formulations of IVD kit reagents and IVD wash solutions.

2) Development of R&D strategy to prevent use of OPEs in new product designs

A global R&D policy was implemented in what was originally the CAI (Chemistry, Automation & Informatics) business division (representing the majority of uses of OPE) to ensure that no diagnostic IVD method achieving final design status post-2013 would contain OPEs. This approach was incorporated into the company's Product Development Process (PDP) and successfully implemented at a global level in the relevant R&D programmes. A communications programme was initiated, with a senior R&D Director in the CAI division given responsibility to ensure that all R&D personnel were aware of the status of OPEs, the policy that they were no longer to be used in any new product-design, and an introduction to identifying suitable alternatives when initiating a Product Development Process (PDP) project. This latter part tied in closely with the third work-stream, the identification of suitable surfactant alternatives.

Detailed examples of the subsequent R&D projects undertaken to replace OPEs in newly-designed products and in existing products are described later in this section.

3) Identification of alternative surfactants for use in IVD products

To support the above policy and to support anticipated future work to phase out OPEs from existing products through re-design, work was initiated to identify surfactant alternatives. It was the assumption at the outset that given the # D of products affected, and the range of

functions that OPEs perform across the global portfolio, a selection of potential alternatives would need to be identified. Subsequent research has confirmed that there is no single alternative which is suitable as a replacement for OPEs in every new or existing IVD product.

Also, given the significant and strictly regulated protocol that must be followed in order to re-design any existing IVD Product, a process which can take 5-12 years (a typical duration of 8 years may be assumed) to complete per product design, it was recognised that any alternative surfactant needed to be 'future-proof' in terms of having a low likelihood of being Restricted or subject to Authorisation under REACH, or under any other regulatory chemicals framework in the # C, D that Siemens Healthineers ships health care diagnostics products to.

Within this work-stream, and taking into account the above recognised factors, the following work was undertaken:

- Consultation was undertaken with the US Environmental Protection Agency (EPA) to collate further data on chemicals with similar technical functionalities but which were not considered hazardous from an environmental or human health perspective. In 2012, the EPA had released a publication entitled Design for the Environment (DfE) Alternatives Assessment of Nonylphenol Ethoxylates on potential alternatives to OPEs, therefore approaching the EPA seemed a logical choice (Siemens Healthineers R&D is also primarily based in the USA and therefore had good visibility of initiatives such as this). The EPA were able to issue information on chemicals which may be considered as suitable alternatives, an excerpt from their communication is shown in **Figure 4-6**.

Figure 4-4: Excerpt from communication with US EPA in efforts to identify suitable low or non-hazard alternatives to OPE

- In May 2014 Siemens Healthineers initiated a collaborative project with the #F bullet point [redacted][7]. The challenge presented by OPEs in terms of the widely impacted Siemens Healthineers product portfolio, and the strong interest in identifying alternatives and potential partners in managing chemicals of concern was presented to a technical team at [redacted]. The institute presented the [redacted] and groups of interest ([redacted]) who could potentially support on this topic. While these links did not initially prove fruitful, dialogue with [redacted] continued, and in May 2015 Siemens Healthineers presented its case at the [redacted] on May 19, 2015. Further discussion was held with [redacted] to discuss work he and his students had already conducted around OPE substitution in other applications.

  This work culminated in the set-up of a research project in 2016. The project was entitled [redacted] and its goals were to:

  Phase 1
  - Develop novel [redacted] surfactants as alternatives to replace OPEs;
  - Demonstrate [redacted] methods using principles of '[redacted]; and
  - Evaluate performance of the [redacted] surfactant in immunoassay applications.

  Phase 2
  - Compare final properties of these [redacted] surfactants to OPEs in the Siemens Healthineers immunoassay product line;
  - Establish overall safety and long-term viability of these [redacted] surfactants in [redacted] tests on primary human [redacted] cells and [redacted]; and
  - Compare biodegradation studies to establish a biodegradation profile.

  The project focused on the synthesis of [redacted] surfactants, i.e. those based on [redacted], and a material was provided for testing in assays at the Siemens Healthineers R&D site at [redacted]. The substances developed and assessed are displayed in **Figure 4-7**.

[redacted]
F

[7] https://www.turi.org/

Figure 4-5: [redacted]

[redacted] # F para [redacted] and [redacted] were chosen to pursue due to their surface tension properties and more favourable toxicity and biodegradation results. This was later narrowed to [redacted] due to a safer, more environmentally friendly and simpler manufacturing process. A summary of the work is included in the report provided in Appendix 4 (Section 12). The first substances supplied were not successful in the testing conducted at the Siemens Healthineers [redacted] R&D site.

This work with [redacted] # F para [redacted] is still ongoing and it is not yet clear if it will lead to the commercial introduction of a viable alternative, however this will continue to be pursued, as it is seen as a long-term project and thus there is currently no set timeline for completion;

- In 2016 a study was commissioned by Siemens Healthineers, working with [redacted] #F para [redacted], to focus specifically on the substitution of octylphenol ethoxylates in IVD kit reagents and IVD wash solutions. [redacted] performed a desk-based analysis of alternatives using information supplied by Siemens Healthineers regarding the function of OPEs in the IVD kit reagents and IVD wash solutions containing OPEs and their technical properties.

  The result of this work was a list of potential surfactant alternatives which Siemens Healthineers R&D were able to use to inform their ongoing work to develop and design new products without the use of OPEs, and to initiate work to reformulate existing products containing OPEs. The list of potential alternatives generated from this work is included in the long-list of potential alternatives established by Siemens Healthineers for consideration in new and existing product design in **Table 4-1** (at the end of this sub-section). [redacted] # F para [redacted] report is available in the Siemens Marburg AfA under EU REACH.

- Internet-based data searches and communications with chemical suppliers were undertaken to understand what alternatives were available on the market, including Merck Millipore & Dow. In recent years, chemical suppliers have released communications based on work undertaken to identify alternatives which offer similar properties to OPEs; Siemens Healthineers R&D teams have been actively monitoring this work and lists resulting from this to initially create a list of alternatives and to continuously update that list.

Of the alternative surfactants identified, profiling of the hazardous properties of each identified substance was conducted with the aim of giving preference to substances which would reduce the overall risk profile. An example of how substances were profiled is presented in **Figure 4-8** below.

		Hazard Class. - ECHA						
Name	CAS.	skin	eye	aquatic	Goodman*	EPA*	Internal	Notes
1-Oleoyl-rac-glycerol	111-03-5	N	N	N			N	
Brij®L23	9002-92-0	Y	Y	N	5			
Brij® O10	9004-98-2	Y	N	Y				
Na Cholate	206986-87-0 361-09-1	N	N	Y			Y	
Decaethylene glycol monododecyl ether	9002-92-0							
Decyl β-D-maltopyranoside	82494-09-5						Y	
Digitonin	11024-24-1	Y	N	N	N	N/A	N	biological, VERY toxic. Avoid
ECOSURF™ EH-9	64366-70-7							
ECOSURF™ SA-9	-							
Genapol® x-080	9043-30-5	N	Y	N	5			aka BRIJ 35
Genapol® 26-L-80	68551-12-2							HLB = 13.4; biodegradable; alcohol ethoxylate
Glucopone	170905-55-2	N/A	N/A	N/A	4			
Kolliphor® P 188 – (3)	9003-11-6	N/A	N/A	N/A	3		N	aka Lutrol® F68
Kolliphor® EL	61791-12-6	Y	Y	N				aka castor oil, ethoxylated
Lauryl Glucoside	110615-47-9	Y	Y	N	4			
Lutensol® XP 80	160875-66-1							
Methoxypolyethylene glycol 350	9004-74-4							
N,N-Dimethyldodecylamine N-oxide	1643-20-5							

Figure 4-6: Example of substance profiling to identify alternatives with a lower hazard category

From the consultation work carried out above with chemical suppliers, the # F para, and known experts in the field of OPE study, combined with the professional knowledge of Siemens Healthineers Method Chemists and their understanding of the performance of other surfactants in other IVD products, the list in **Table 4-2** presents those surfactant alternatives which Siemens Healthineers has actively considered and/or actually tested in certain IVD Products. It is important to note again that no single one of these would be suitable for all impacted IVD Products due to the range of technical functions of the surfactant and the biological variability an IVD product must adapt itself to when testing for certain diseases or conditions.

Table 4-2: List of OPE alternatives which could be suitable for IVD Products based on the various branches of work conducted by Siemens Healthineers to identify suitable alternative surfactants

Name	CAS Number	Tested in Siemens Healthineers IVD Product?
Triton™ X-100	9002-93-1 / 9036-19-5	Reference
1-Oleoyl-rac-glycerol	111-03-5	# F table
Brij® L23	9002-92-0	
Brij® O10	9004-98-2	
Brij® 35	9002-92-0	
Decaethylene glycol monododecyl ether	9002-92-0	
Digitonin	11024-24-1	
ECOSURF™ EH-9	64366-70-7	
ECOSURF™ SA-9	-	
Genapol® X-080	9043-30-5	
Kolliphor® P 188	9003-11-6	
Kolliphor® EL	61791-12-6	
Lutensol® XP 80	160875-66-1	
Methoxypolyethylene glycol 350	9004-74-4	
N,N-Dimethyldodecylamine N-oxide	1643-20-5	
n-Dodecyl β-D-maltoside	69227-93-6	
n-Nonyl-β-D-Glucopyranoside	69984-73-2	
n-Octyl-β-D-thioglucopyranoside	85618-21-9	
Nonaethylene glycol monododecyl ether	3055-99-0	
Pluronic® F-127	9003-11-6	
Pluronic® F-68	9003-11-6	
Pluronic® 25R2	9003-11-6	

Table 4-2: List of OPE alternatives which could be suitable for IVD Products based on the various branches of work conducted by Siemens Healthineers to identify suitable alternative surfactants		
Name	**CAS Number**	**Tested in Siemens Healthineers IVD Product?**
Pluronic® 31R1		[redacted]
Pluronic® L64		[redacted]
Poly(ethylene glycol)	25322-68-3	[redacted]
Polyoxyethylene (10) tridecyl ether	78330-21-9	[redacted]
Saponin	8047-15-2	[redacted]
Silwet 7604	-	[redacted]
Silwet 7606	-	[redacted]
Span® 80	1338-43-8	[redacted]
Span® 85	26266-58-0	[redacted]
TERGITOL™	68551-14-4	[redacted]
TERGITOL™ 15-S	68131-40-8	[redacted]
TERGITOL™ NP	127087-87-0	[redacted]
TERGITOL™ TMN	60828-78-6	[redacted]
Tetramethylammonium hydroxide pentahydrate	10424-65-4	[redacted]
Thesit®	9002-92-0	[redacted]
Triton™ X-100, Reduced	92046-34-9	[redacted]
Triton™ X-114, Reduced	92046-34-9	[redacted]
Triton™ X-405, Reduced	92046-34-9	[redacted]
Tween® 20	9005-64-5	[redacted]
Tween® 60	9005-67-8	[redacted]
Tween® 80	9005-65-6	[redacted]

A number of the alternatives listed above have been actively tested by Siemens Healthineers R&D in a number of new product development projects and in the re-design of existing products.

Below is a list of Siemens Healthineers IVD Products that have successfully achieved final design since 2013 with the use of an OPE alternative and referencing the specific surfactants chosen:

[redacted]

D, F bullets

[redacted]

[redacted]

– [redacted].

The following are examples of the extensive R&D projects which were undertaken specifically to design new, or re-design existing, IVD products with the aim of making them OPE-free.

OPE Alternatives Project – Example 1

- **<u>Wash Solution Re-Design - Basic description of the project</u>**

The # D portfolio of immunoassay products are run on dedicated systems, which require for their operation a cleaning solution called Probe Wash. The Probe Wash facilitates the cleaning of the system probes that are used to pipette patient samples and assay reagents. The Probe Wash solution requires a non-ionic surfactant as part of its formulation. The surfactant used was Triton X-100, which in recent years has been added to the Substances of Very High Concern list under the EU REACH legislation due to its environmental impact on aquatic life. This project was scoped to identify an alternative surfactant to Triton X-100 and subsequently to qualify and implement the chosen replacement as part of the Probe Wash formulation.

- **<u>What alternatives were tested, which one was successful and why (if known)</u>**

As part of an initial screening exercise, 21 potential replacement surfactants were identified and evaluated through an assessment of their physicochemical properties. The 2 most promising candidates identified were then scrutinised via laboratory testing of their efficacy within the Probe Wash solution. This testing identified a surfactant known as Brij58 as a potentially feasible candidate, since this surfactant exhibited similar physicochemical properties, acceptable probe washing performance and cost/availability of material.

Test pilots of the Probe Wash containing the Brij58 replacement surfactant were manufactured, and the efficacy of the new Probe Wash was verified to have no detrimental impact on system probe washing. This involved testing all # D assay products (# D products in total), whereby the functional performance areas of accuracy, precision, sensitivity and carryover were evaluated. This assessment confirmed the feasibility of replacing Triton X-100 with Brij58 in the Probe Wash formulation.

In order to implement the new Probe Wash, design change verification testing was performed whereby multiple lots of the reformulated Probe Wash was tested for equivalence to the current Probe Wash using worse-case challenge conditions. In addition, real-time shelf-life stability studies were required in order to verify the 2 year shelf-life of the product.

- **<u>Any challenges, including technical, administrative, global project management etc</u>**

The major challenges associated with the project were:

- Identifying an alternative surfactant that exhibited similar physicochemical properties, acceptable probe washing performance and cost/availability of material.
- As the product is a critical consumable for the daily operation of the assay systems, the change impacted the entire # D product portfolio resulting in the testing of 190 assay products. This required significant technical and manufacturing resources to support the verification process.
- Ensuring that the project was delivered to the timeline communicated to REACH with regards to the replacement of Triton X-100 in the Probe Wash formulation.
- Verifying the 2 year shelf-life stability of the product.

- **<u>Any lessons learned</u>**

Advantageous to develop an efficient strategy to facilitate high-throughput testing and analysis work in order to best utilise available resources and to meet challenging timelines.

Advantageous to identify multiple potential alternative materials in order to mitigate any raw material supply challenges that may occur during the course of a project.

OPE Alternatives Project – Example 2

IVD Product Name	# B, D, F Table Assay
Product Description	The) assay is for *in vitro* diagnostic use in the quantitative measurement of in human serum or plasma ( ) using the Analyser. The assay can be used to aid in the diagnosis of acute)
New or Existing Product?	New
Year Development Initiated	2011
Development Location	Siemens Healthcare
Development Team	Assay Development Team,
Background	The initial reagent design contained % (w/w) Triton™ X-100, which performed excellently, however, as with the previous example, the anticipated inclusion of OPE on the Annex XIV list led the R&D team to initiate a project to identify an alternative.
Alternatives Tested	Tween® 20 Brij® 35 Silwet 7604 Silwet 7606 Pluronic 25R2 Pluronic 31R1 Pluronic L64 Tween® 80
Summary of Analysis	Several candidate alternatives initially worked well during early screening, but additional testing proved more challenging. The basic screening consisted of . The idea was to maximise the and the assay , removing as well. A few low end were also added to collect and . Background was also an important consideration, there should not be any non-specific binding (NSB) that generates signal in the absence of analyte. In comparing assay performances with the OPE and with an alternative, examination of several fundamental metrics/behaviours were undertaken, such as) with the two formulations and sample recovery comparisons. A portion of each detergent formulation was also set aside to check and . When another critical IVD performance parameter, , was checked with the formulation containing Silwet 7604, the new formulation did not pass. Unfortunately, this was the only OPE alternative to show acceptable performance for many of the other critical parameters. This issue was finally remedied by switching to the . Finally, it was necessary to label with all available s

	and understand the influence of [redacted] and [redacted]. [redacted] was the only one that was effective but it also incurred issues - the [redacted] stuck to the [redacted] as it was not [redacted] completely. As a result, over time on replicate measurement using [redacted], the [redacted] reagent became irreversibly [redacted] raising the background. The addition of [redacted] to the [redacted] whose [redacted] mimic [redacted] and increasing the probe's [redacted] at the wash station solved the problem
Summary of Results	Replacing Triton™ X-100 not only required finding an acceptable alternative, but also resulted in a new detection label ([redacted] and further [redacted]. In total, all these efforts to identify an alternative to [redacted]he OPE added a year to the development of the [redacted] assay.

OPE Alternatives Project – Example 3

IVD Product Name	# B, D, F Table
Product Description	The assay is for *in vitro* diagnostic use in the quantitative determination of) in human serum and plasma ( ) using the Analyser. Measurements of produced by the are used in the diagnosis of disorders. The commercial assay in an important test and requires one of the lowest in the portfolio
New or Existing Product?	Existing
Year Development Initiated	2016
Development Location	Siemens Healthcare,
Development Team	CPS Team, R&D,
Background	This product contains OPE in each of three separate reagents that constitute the product. In this example, therefore, three reagents need to be reformulated and very stringent acceptance criteria must be met.
Alternatives Tested	Alternative concentrations of OPE Removal of OPE Tween® 20 Tween® 60 Silwet 7604 Triton™ X-100 Reduced
Summary of Analysis	The initial experiments tested three conditions; to lower the OPE concentration to below the REACH threshold level (to use the threshold level and to . The results clearly demonstrated that none of these conditions were acceptable due to poor precision, LoD failures and loss of Functional Sensitivity. Importantly however, these initial studies demonstrated that one reagent of the three was the main contributor to the performance failures. The development chemist then focused on the reagent having the greatest impact on performance and tested four different concentrations of the following surfactants: Tween® 20, Tween® 60, Silwet 7604 and Triton™ X-100 Reduced. Overall, optimal concentrations were identified for each of these alternatives that at this preliminary stage yielded similar, or in a couple of instances better, performance for LoD and Functional Sensitivity. Multiple candidate formulations will be prepared in the next stage of this project and these will be subjected to much more thorough testing, including real-time stability studies
Summary of Results	Although preliminary studies were promising, additional assay performance characteristics will also be addressed in the re-formulation process so a new study was initiated in 2018

Overall summary of alternative testing by Siemens Healthineers

Note that for commercial OPE-containing products or those that have already obtained final design status (as described above), only select feasibility testing has been conducted by Siemens

Healthineers. The strategy is now to determine the efforts required to identify potential alternatives to Triton™ X-100 in # F, G. While there are examples of this being completed successfully, there are also examples where it has been demonstrated that known and tested alternatives are not acceptable substitutes.

Each assay product's design is unique and each one must be fully tested to confirm that an alternative is acceptable. There are no guarantees of success at the outset of this process, even if an alternative substance has been successfully (or unsuccessfully) proven for a similar assay. As described above, therefore, physico-chemical properties and toxicological classification of potential alternatives are aids in prioritising the order in which alternatives are evaluated. This has been used in practice. However, due to the complex and unique nature of each milieu, as well as the potential multiple effects that OPEs convey to IVD assay performance, there is no single alternative that has been shown to be a universal replacement. Differences among the IVD products arise from the different critical raw materials (i.e. antibodies, signal technology, etc.) which manifest unique biological and physiochemical characteristic to the products. As such, each product behaves in a different way and has different performance characteristics. The reason for this is due at least in part to molecular interactions between the chemicals and the proteins involved, but inadvertent reactions cannot always be predicted as explained earlier in this section when describing the technical challenges. Each product is therefore produced by following a unique and product-specific protocol.

The efforts undertaken as part of the extensive work done by the Siemens Healthineers organisation to identify alternative substances to OPE continually benefit future efforts. Consequently, after careful consideration of the above parameters, it is concluded that several alternatives, alone or in combination, must be systematically and experimentally evaluated on a 'per product' basis so as to be able to successfully implement alternatives across the # D Siemens Healthineers portfolio.

Past and current research and development by Downstream Users

It is unclear what efforts end users of IVD kits may have initiated. A few customers of Siemens Marburg have actively approached the applicant to enquire as to how Siemens Healthineers are planning to manage the REACH Authorisation of OPEs. This indicates that there is some expectation that suppliers will take care of either substitution or Authorisation of continued use of OPEs to ensure diagnostic activities can continue without interruption. Currently there is no information available if and what efforts end users of IVD kit have initiated to identify alternatives besides such enquiries.

However, it is important to note Siemens Marburg believes that DUs have limited opportunity and capability to undertake meaningful R&D on alternatives for OPEs for the following reasons:

- **R&D capabilities on chemical substitution and IVD kit development**: DUs do not typically function as developers of diagnostic technology, and do not sell diagnostic platforms themselves. Without access to the protected diagnostic technology of the analyser platform they own, they would first need to develop their own diagnostic technology and platform before designing an OPE-free IVD kit. Given the significant number of years this would take to develop this technology, commercialise a product and presumed lack of a current R&D function with this capability, this does not seem like a viable or plausible approach for customers;

- **Access to raw materials:** any attempt to modify existing technologies (IVD kits and analysers) would also suffer from a lack of access to relevant raw materials. This is especially the case for active IVD kit ingredients as antibodies or other relevant proteins which are normally a highly specialised supply. Besides the engineering knowledge needed for the production of the analyser, this is another core expertise often protected by patents and therefore not accessible to third parties. In consequence, a hospital or a similar institution would not have the raw materials to perform any testing to change existing technology. Hence it is not possible for any DU of an IVD kit to initiate substitution activities of a substance by an adaptation of the IVD kit components or the analyser technologies themselves. In the theoretical situation that such an institution would be able to achieve a substance substitution or similar, it would also need to perform the registration process required for IVD products in order to be able to use the adapted IVD kits (or analyser), again an activity that would take several years; and

- **Knowledge of regulatory requirements is limited**: DUs typically have limited awareness and knowledge of the regulatory status of the design and placing on the market of IVD kit reagents and wash solutions. As a consequence, it can be reasonably assumed that downstream users know little about REACH Authorisation or alternative detergents. Even if they have been aware of the issue of REACH Authorisation of OPEs, they would not be capable of initiating any meaningful research and development activities aimed at the substitution of OPEs and would normally approach their suppliers for advice on the matter.

This lack of awareness and capability on the part of DUs is one main reason for Siemens Marburg deciding to submit an upstream AfA for the continued use of the IVD kits and wash solutions in the EEA. It also means that only research and development from Siemens Healthineers' perspective is of relevance to the discussion presented in this AoA-SEA document.

4.1.2 Data searches

The website/data searches conducted to identify OPE alternatives are listed below. It should also be noted however that many of the afore-mentioned alternatives were identified based on the expert knowledge of R&D technical staff from their experience in using a wide range of surfactants in IVD products.

- Siemens Healthineers internal databases, i.e. SAP, R&D databases;

[redacted]

- [redacted]

Searches focused on alternative (OPE-free) IVD kits

Siemens Marburg has researched the market for third-party IVD kits that cover the same assays to establish whether OPE is mentioned as component of the kit reagent in the respective Safety Data Sheets. These searches have generated information that can only be considered a snapshot of the situation at the end of 2018 and does not reflect any contemporaneous efforts that Siemens Marburg's competitors may be making towards the reformulation of their IVD kits or indeed the Authorisation of their continued use of OPE. The following table presents the findings of these searches for selected IVD kits that fall within the scope of the present AfA. It can be seen that for some kits, third-party replacements would also contain OPEs. It should be noted that such kits would normally need to be used on third-party analysers, they cannot simply be used as drop-in replacements on Siemens Healthineers analyser platforms.

Table 4-3: Presence of OPE in IVD kit reagents placed on the market by Siemens Marburg's competitors

Assay	[redacted]	[redacted]	[redacted]
# Cm D [redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

4.2 Identification of known alternatives

In the "Applied for Use" Scenario, the DUs of Siemens Healthineers and Siemens Marburg will be supported in phasing out OPEs through the future introduction of OPE-free IVD products which will gradually replace the OPE-containing ones currently in use. The research and development and product realisation work will be done by Siemens Healthineers, with OPE-free products introduced to market as per the REACH Response Plan timelines presented in Section 6.3.

In the "Non-use" Scenario, Siemens Healthineers' customers would be required to take immediate action to identify alternative solutions, each resulting in significant cost and disruption to the healthcare diagnostics system. These alternative scenarios are listed below and further described in the subsequent sections. These following theoretical alternatives are based on Siemens Healthineers' own knowledge of customer requirements and information provided by a number of customers who use the impacted IVD products through a surveying exercise:

1. Replacement of the OPE-containing component of an IVD product (e.g. the IVD kit reagent and/or IVD wash solution) with an OPE-free component.
2. Replacement OPE-containing IVD kits with analyser-compatible OPE-free IVD kits.
3. Purchase of new analysers that only use OPE-free IVD kit reagents or IVD wash solutions.
4. Outsourcing of the tests that depend on OPE-containing IVD products to a third party.
5. Cessation of diagnostic operations which involve the use of OPE-containing IVD products.

These scenarios are discussed in detail below in order to identify the most realistic "Non-use" Scenario for the downstream users, which will form the basis for the impact assessment in Section 5 of this AoA-SEA document.

4.3 Assessment of shortlisted alternatives

4.3.1 Alternative 1: Replacement of the OPE-containing component of an IVD product

This scenario considers the possibility of sourcing another OPE-free component to replace the part of the IVD kit which contains OPEs, or for customers to design their own IVD product kit reagent or wash solution.

Substance ID, properties, and availability

Siemens Healthineers does not produce interchangeable IVD kit components that would serve different IVD kits (as explained below) and therefore it is not possible to list a substance or substances in this section which would be relevant.

If, hypothetically-speaking, a like-for-like competitor OPE-free IVD kit component were available, the alternative surfactant could be any of those available on the market today and would only be known by the IVD company producing that particular IVD kit component.

Technical feasibility of Alternative 1

Use #1 & Use #2

The IVD kit reagents and IVD wash solutions provided in or with Siemens Healthineers IVD kits have been specifically designed and extensively tested to work in combination with the other components of the kit they belong to; this includes any other IVD kit reagents in the kit, any accompanying

calibrator and diluent components, and also the IVD wash solutions used on the analyser with all the IVD products within an analyser platform.

To Siemens Healthineers' knowledge, there are no alternative IVD kit reagents available on the market which are designed to be used in combination with other components of an OPE-containing IVD kit. There are other IVD wash solutions on other Siemens Healthineers or competitor platforms which technically a customer could use as an OPE-free alternative; however, this would not be an advisable approach and could significantly affect the performance of the IVD kits and generate inaccurate patient test results.

Also, it would not be feasible for a customer to try and re-design an IVD kit reagent or IVD wash solution to work with other components of a Siemens Healthineers IVD kit. From a technical perspective this would not be possible without a full knowledge of the technology which allows the IVD product to function. Customers are experts in the field of providing diagnostic results to healthcare providers, typically they are not IVD companies with R&D departments dedicated to the development of IVD technology.

Economic feasibility and economic impacts of Alternative 1

Use #1 & Use #2

As shown above, Alternative 1 is technically infeasible and thus realistically impossible to implement:

- If OPE-free IVD kit reagents and wash solutions were currently available on the UK market, they would not be compatible with (most) Siemens Healthineers' IVD kits and analysers. This means that the customers would have to replace the analysers and IVD kits they use, or outsource (parts of) the diagnostic tests they undertake. These options are described in more detail under Alternative 3 and Alternative 4 below; and

- If OPE-free reagents and wash solutions do not exist on the UK market before the UK Sunset Date, Siemens Healthineers' customers would have to discontinue testing until OPE-free products became available, or outsource (parts of) the diagnostic tests to laboratories outside the UK. These options are described in more detail under Alternative 4 and Alternative 5.

In summary, the economic feasibility of this alternative is impossible to describe in monetary terms as its implementation is technically infeasible.

Availability of Alternative 1

Use #1 & Use #2

As stated above, there are no alternative IVD kit reagents available on the market which are designed to be used in combination with other components of an OPE-containing IVD kit.

There are other OPE-free IVD wash solutions available on other platforms, however they are not proven to be compatible with any IVD products on other analysers apart from those for which they are designed. To test this compatibility and prove no performance issues, Siemens Healthineers would need to initiate a Design Change Project and conduct feasibility and stability testing against every IVD product used on that analyser, and then apply for re-registration of the IVD wash solution

as is the regulatory requirement. This process would take several years; customers would not be able or willing to wait for this process to be completed and thus would seek alternative solutions.

The process of re-registration of IVD products is described in more detail in Section 4.3 of the AfA submitted by Siemens Marburg for Applied for Uses #1-3.

Hazard and risk of Alternative 1

Use #1 & Use #2

A general evaluation of an OPE-free alternative IVD kit reagent is not possible at this time, since there are no known IVD kit reagents and/or IVD wash solutions proven to work as an alternative to any OPE-containing IVD product placed on the EEA market by Siemens Healthineers.

Conclusions on Alternative 1

Use #1 & Use #2

In summary, this is not considered to be a feasible alternative for customers using OPE-containing IVD kit reagents and/or IVD wash solutions as stand-alone OPE-free components which are compatible with all other components of the IVD kit and the analyser systems are not available on the market to Siemens Healthineers' knowledge. Even if one would consider using currently available OPE-free wash solutions as replacements for the OPE-containing ones, the feasibility and stability testing against every IVD product used on that analyser that would be required would render this option incompatible with the business needs of the customers.

For customers to reformulate their own OPE-free versions is also not a feasible option as they are not typically set up as IVD technology and/or manufacturing companies with the resources immediately available to conduct IVD development work.

For these reasons, this alternative is extremely unlikely to materialise before the UK Sunset date for either Use #1 or Use #2.

4.3.2 Alternative 2: Replacement of OPE-containing IVD kits with OPE-free IVD kits which are compatible with existing analysers

This scenario considers the possibility of sourcing another OPE-free IVD kit which performs the same tests as the IVD kits which contain the IVD kit reagents and IVD wash solutions in the scope of this AfA, and using these on the Siemens Healthineers analyser platforms in place at the customer sites.

Substance ID, properties, and availability

There are no OPE-free IVD kits in the Siemens Healthineers portfolio that could be used as drop-in replacements for the OPE-containing IVD kits.

Whilst there may exist OPE-free IVD kits providing the same diagnostic tests available from competitors in a limited number of cases, their existence, characteristics and performance are by large unknown to Siemens Healthineers (NB. **Table 4-3** has shown some preliminary market research undertaken by Siemens Healthineers which suggests that several competitor IVD kits may also contain OPEs).

For the reasons above, an alternative substance cannot be discussed here.

Technical feasibility of Alternative 2

Use #1 & Use #2

While in some cases there are alternative IVD kits available within the Siemens Healthineers portfolio which offer the same diagnostic tests, each kit is designed to be used on a specific platform and/or analyser within that platform and they are not interchangeable. For example, a customer using an [redacted] IVD kit to test for [redacted # D para] on their [redacted] analyser, could not buy the [redacted] IVD kit for [redacted] and start using it on their [redacted] analyser. The physical set-up of the analyser would not accept the type and size of the [redacted] components, the immunochemical technology is completely different (e.g. [redacted] uses [redacted] beads held in a separate component and which are analysed in a separate part of the machine to the reagent, whereby the [redacted] technology means the solid phase is suspended in the reagent itself). In conclusion, it would not be possible for customers to source Siemens Healthineers OPE-free IVD kits to replace any of the Siemens Healthineers OPE-containing IVD kits and use them on their existing analyser systems.

Analysers/systems are either 'Open' or 'Closed' channel, which indicates whether a third-party IVD kit could technically be used on that analyser should one be specifically designed for that purpose by a competitor. It is possible that for some of the 'open channel' analyser systems, e.g. the [redacted #D para] platforms, there may be third-party IVD kits available which are OPE-free and could be used on the system. Closed systems, e.g. [redacted] and [redacted] platforms will not work with any IVD kits other than those designed by Siemens Healthineers. Typically, the clinical chemistry systems are open while the immunoassay systems tend to be closed (although there are exceptions).

However, while this possibility to use third-party IVD kits exists on the 'open channel' analysers, there are some key factors to note:

- It is not known by Siemens Healthineers which of the OPE-containing IVD kits have OPE-free (if any) alternatives providing the same diagnostics tests – customers would have to conduct market research to identify alternative IVD kits and determine whether they contain OPEs. This would likely take some time; while DUs are searching for alternatives and then implementing them, patient samples either could not be tested at all if no alternative, OPE-free kits are available, or samples would have to be sent out to another lab. This would then delay test result and make emergency testing impossible in the immediate aftermath of a refused Authorisation;

- Searching for alternative supplier reagents may be locally difficult, as not all reagents are available in all countries (i.e. through local suppliers);

- If any third-party IVD kits providing the same diagnostic tests were sourced, customers would be responsible for performing validation of third-party tests on the analysers and confirming performance parameters. This can take a significant amount of time and delay results, particularly in larger labs where larger groups of people may need additional training. Alternative IVD kits could produce different reference ranges, which are used by healthcare providers/physicians to assess results and provide diagnoses. New reference ranges mean a

significant communication exercise throughout the healthcare system to ensure results are not mis-read and thus incorrect diagnoses are made;

- Adaptation of the reagents to the system ("method") only works with specific assay parameters that can require a significant development and validation effort by the customer. The IVD compliance development, testing and documentation typically takes 6-24 months[8], depending on the complexity of the method. Of course, after having developed the new methods, a correlation of the new vs. the old (discontinued) method would be required. This is needed to ensure normal samples as well as pathologic samples are identified correctly. This includes the achievement for comparable results especially for the follow up of patients. This implies that the old material remains available for testing after the adaptation work is done; and

- It should be noted that Siemens Healthineers is currently working on implementing its REACH Response Plan for the phase out of OPEs so that all IVD kits offered will have an OPE-free alternative available; however, this will not be in time for the June 2022 UK Sunset Date and is therefore not relevant for the "Non-use" Scenario. The complexity of substituting OPEs for the full range of products in the Siemens Healthineers portfolio is significant, as described in Section 4.1, and therefore, such substitution will happen over an extended period of time.

It is worth noting the complexities that would arise for certain among Siemens Healthineers customers. In the case of research centres/universities, these customers might need to restart their research as the output data would change once third party IVD products were introduced.

Economic feasibility and economic impacts of Alternative 2

Use #1 & Use #2

As a general assumption, market prices are comparable between Siemens Healthineers and third-party assays (IVD kits/wash solutions) and analyser platforms. However, specific pricing information is not generally publicly available as the cost depends on the individual contract between the supplier and the customer (the cost can differ depending on a number of factors, e.g. if replacing another system, the number and type of IVD kits the customer will be purchasing, the length of the contract, etc.) and qualify as trade secrets of the involved parties. As such, if third-party OPE-free IVD kits and wash solutions were available on the UK market, the economic impact of transitioning to those kits/wash solutions could be low.

The reality, however, is that compatible third party IVD kits and wash solutions are not available from Siemens Healthineers neither can they be made available for 'closed channel' analyser platforms. For 'open channel' platforms, the existence of compatible third-party OPE-free IVD kits and wash solutions cannot be confirmed and even if they did exist their validation and subsequent adaptation of the new reagents to the system would be a prolonged process. Over this period,

[8] This testing activity needs to be distinguished from the activities aimed at finding an alternative substance. Here the testing refers to a testing of an already developed IVD kit system and its adaptation to a Siemens Healthineers analyser.

customers could not deliver the diagnostic test services that currently rely on the operation of the Siemens Healthineers analysers.

This means that the customers would have to either replace the analysers and IVD kits they use or outsource (parts of) the diagnostic tests they undertake. These options are described in more detail under Alternative 3 and Alternative 4 below.

Depending on which Siemens Healthineers IVD product was discontinued, the existing analyser would economically be rendered unusable (especially in the case of a wash solution). The analysers could be used for the remaining assays that are not affected by REACH Authorisation requirements. However, as lab space is normally limited, customers generally try to consolidate as many different assays as possible on one analyser. Most customers would find it difficult to operate two or more analysers if they could not find a replacement for their Siemens Healthineers analyser that could run all assays.

In summary, the economic feasibility of this alternative is likely to match that of Alternatives 3 and 4 and a more detailed analysis of the associated economic impacts is presented under each respective alternative below.

Availability of Alternative 2

Use #1 & Use #2

It would not be possible for customers to source Siemens Healthineers OPE-free IVD kits to replace any of the Siemens Healthineers OPE-containing IVD kits and use them on their existing analyser systems.

As discussed above, neither Siemens Healthineers nor third-party IVD kits are available for 'closed channel' analysers, as these cannot be operated without the specific OPE-containing IVD kits in scope of this AfA for those particular diagnostic tests.

The availability of third party IVD kits for 'open channel' analyser systems is not known. As discussed above, it is theoretically possible that these IVD kits are available; however, Siemens Healthineers are not aware if any specific IVD kits containing alternative IVD kit reagents or IVD wash solutions are available on the market. From a theoretical point of view, one can state that there is no strong incentive for a third-party producer to develop an IVD kit for Siemens Healthineers analysers as most market actors in this field share a core strategy of selling analysers together with own IVD kits. Therefore, research and development is generally directed towards developing one's own product portfolio to improve one's own market position, rather than to develop IVD kits that are compatible with competitors' analysers.

Overall, the availability of compatible IVD kits is expected to be poor.

Hazard and risk of Alternative 2

Use #1 & Use #2

Given that alternative OPE-free IVD kits are not available in most cases, i.e. not marketed by Siemens Healthineers and cannot be used on 'closed channel' analysers, and that where they may

theoretically be available they are not known to Siemens Healthineers, a general evaluation of the hazard profile of an alternative detergent used in an alternative IVD kit is not possible.

Based on feasibility testing so far done by Siemens Healthineers, and described in Section 4.1, there are a number of detergents with a lower hazard profile than OPEs available and which have shown some success in the re-design of IVD products thus far.

Conclusions on Alternative 2

Use #1 & Use #2

it is unlikely customers could turn to this alternative in the event of non-Authorisation. Even if some third party IVD kits were found by customers to be available for the 'open channel' analysers, it would take time to adapt to using these alternative kits, with potentially some change to methods, performance, reference ranges and therefore training and communications throughout their downstream supply chain in the healthcare system, which would cause delay and occupy resources which would be better allocated to disease diagnosis and patient care.

In real life, customers would not able or willing to endure a long period of inability to offer diagnostic services; therefore, it is extremely unlikely that they would opt for this alternative on the Sunset Date.

4.3.3 Alternative 3: Purchase of new analysers that only use OPE-free IVD kit reagents or IVD wash solutions

Alternative 3 evaluates the option for the customer to switch to an analyser platform that exclusively uses OPE-free IVD kit reagents and IVD wash solutions.

Substance ID, properties, and availability

Given that any alternative platform or analyser that a customer could potentially purchase under this scenario is not known (as it entirely depends on each customer's needs), and that any platform would likely use a range of alternative detergents across the range of IVD products available on any selected analyser, it is not possible to identify a specific alternative substance to discuss in this section. As the use of OPEs in the IVD industry is fairly common, it seems unlikely for most customers that alternative suppliers would only provide OPE-free products for the wide range of different tests falling within the scope of the Applied for Uses.

Technical feasibility of Alternative 3

Use #1 & Use #2

A typical customer in a large hospital reference lab may be running multiple analysers from a particular platform, or potentially a range of analysers from different platforms. Faced with the situation whereby they can no longer utilise some or all of their existing analysers because the tests they need to run contain OPEs, these are the steps they would need to follow to purchase new analyser systems:

1. **Define their testing needs**: this would require a full review of all the tests they are required to perform across the range of analysers currently in use, looking at numbers and types of

tests, throughput, turnaround times, performance requirements, reference ranges, available staff numbers, etc.

2. **Analyser capacity**: this could potentially be compared to 'building a new house'; plans and schematics are normally drawn up of the laboratory areas to calculate how much space is available. Analysers, and especially groups of analysers, can take up quite a lot of space, as well as the adjacent space required for peripheral services for sample prep, hand-washing, waste management, etc.

3. **Put the contract out to tender**: IVD companies (suppliers of analysers) are invited to tender. The laboratory's requirements are reviewed, analysers within each supplier's range are identified and confirmed as to whether they meet the customer's needs from a testing and capacity perspective. This can involve several rounds of site visits and exchanges of information to ensure all needs are fully known and understood.

4. **Discuss contract details**: contractual arrangements are discussed, for example the ongoing purchase of IVD products for specific analysers (i.e. IVD kit reagents and IVD wash solutions), pricing, contractual terms and periods, ongoing sales and service arrangements, etc.

5. **Delivery and installation**: once a contract has been agreed, delivery and installation of the analyser systems take place. This can sometimes involve civil work to cater for any changes in layout or analyser size, to ensure a power supply, access to water and potentially to accommodate waste or drainage arrangements. In addition, a period of validation based on the customers' Quality Management System would be required after installation and before the start of routine testing. For larger installations this can take 8 weeks or more.

6. **Training**: training on the safe and effective operation of the new analyser systems is arranged and takes place, normally provided by the supplier IVD company.

7. **Adaptation to local procedures**: local procedures in the laboratory are updated and training on any changes are documented.

8. **Follow-up communication**: communications are arranged by the customer to their healthcare provider network to ensure any changes, for example reference ranges or turnaround times, are fully understood and incorporated into any of their local procedures or required documentation.

The above tendering process through to completion normally takes longer than 12 months, often up to 2 years in the case of larger laboratories.

Providing all of the above steps were followed systematically, as is normally the case, it can be assumed the introduction of this alternative could be accomplished without a decrease of diagnostic performance of a healthcare institution.

Economic feasibility and economic impacts of Alternative 3

Key assumptions

Siemens Healthineers' analysers typically have a lifetime of # D (range: 5-20) years. Changing to a new platform at the Sunset Date means that a number of customers would have to invest in a new analyser before the end of life of their existing analyser.

The approach taken to quantifying the costs for those DUs that currently have a Siemens Healthineers analyser is based on the following[9]:

- For the existing stock, the average estimated remaining life of the analysers is determined for 2022, with this then compared to the typical lifetime of each analyser platform to determine the residual value that would be if the analysers were prematurely replaced. This approach takes into account the fact that some of the analysers in use in the UK were purchased several years ago and would be due for replacement during the requested 12 year review period;

- Since the third-party analysers exists in the same market as Siemens Healthineers' analysers, it is reasonable to assume that the prices of the third-party analysers are similar in price to that of Siemens Healthineers ones. A typical price for a Siemens analyser is between # D (range: £10,000-100,000), . The analyser prices are also assumed to grow with the same pace as the inflation, which means that the real prices are assumed to be constant throughout the review period;

- This premature investment will lead to additional costs for Siemens Healthineers' customers, not only associated with the costs of the new analysers but also in foregone investments in other equipment/projects that would yield a return (whether financial or in terms of improved health care and efficiency). This lost yield is reflected in the discount rate the actor uses when deciding to invest in an asset or not. Siemens Healthineers' customers are diverse, spanning both commercial and not-for-profit actors, so it has not been possible to obtain a common interest rate that reflects the alternative costs in the sector. For the purposes of this analysis a discount rate of 3.5% has been used. Expenditure is assumed to take place in 2022 and the additional cost due to premature investment is estimated in terms of discounted value of the analysers remaining life. The example in **Box 4-1** shows that the costs of premature investments depends on the remaining life time of the analysers, the price and the discount rate (yield).

[9] The sale of analysers is far more complicated than these simple calculations suggest. For instance, these calculations ignore the commonly used business model of seeding instruments (i.e. placement for free and financed through reimbursement for reagents). This business model could exacerbate impacts on Siemens Healthineers' customers under the "Non-use" Scenario. Arguably, the cost for customers in seeding models might be even higher compared to a purchase of instruments or at least at the same level as the reagent prices would include the costs of the provision of the instrument. Given the significant variation in these types of contracts and lack of available data to support this type of analysis, the current calculation is considered the most appropriate approach.

Box 4-1: Example calculation of costs of premature investment

A laboratory owns an analyser with an expected remaining life-time of five years. By way of hypothetical example, say, the price of a new analyser was £60,000 and the real price is not expected to change in the medium term. The expected return on investment available in the market during that period is 3.5% per year. This means that, if the laboratory invests £60,000 today, it would have £60,000*1.035^5 = ca. £71,260 after five years. Under Alternative 3, the laboratory would have to buy a new analyser today and will therefore not be able to invest the £60,000 in other investments. After five years, the laboratory has then lost the equivalent of £71,260 - £60,000 = ca. £11,260 in gains from other investments. The additional costs due to premature investment in the analyser under Alternative 3 is therefore ca. £11,260.

By comparing the average of the stock of analysers with the expected lifetime, it is possible to calculate the remaining life years and residual value of the analysers, which indicates how premature the investment is (in years).

Use #1 & Use #2

Table 4-4 summarises the calculations of the cost of premature replacement of the existing stock of analysers in the UK which are known to be relevant to the OPE-containing IVD kits and wash solutions relevant to Uses #1 and #2. Only analysers that still have over 3 years of expected service life left have been taken into account (those with less than 3 years are not considered as their replacement would not be as burdensome under the "Non-use" Scenario).

Overall, under the Non-Use Scenario, # D analysers relevant to Use #1 and # D relevant to Use #2 (range: 100-400) analysers would need to be replaced prematurely. This would cost the current users of these analysers # D million (range: £5 - 25 million) in 2022 prices. As some of these analysers were purchased several years ago and would be replaced during the review period, it is more appropriate to consider the residual value of the existing stock of analysers. Based on the figures given in Table 4-4, the residual value of downstream users' existing analyser stock is estimated at # D million (range: £5 - 25 million) in 2022.

Table 4-4: Total costs of premature replacement of analysers relevant to Applied for Uses #1 and #2

Type of analyser	No affected Range: 50 – 200	Expected lifetime Range: 5 – 20	Average remaining life – 2021 Range: 0 - 10	Average price (£ 2021) Range: £25,000 – 75,000	Lost residual value due to premature replacement Range: 20,000 – 40,000	Total lost residual value due to premature replacement (£ 2021) Range: £5 – 15 million
Use #1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	# D, E
Use #2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					Total	[redacted]

Note that the avoided capital costs for the customers are not dependent on whether they buy the analysers from Siemens Healthineers or from another company. They are the costs of the premature need to replace the current stock of affected analysers, although the switch to other suppliers' equipment will usually require additional effort, e.g. towards training the lab personnel. It

is also anticipated that the costs of non-Siemens IVD kit reagents and wash solutions would be generally similar to those of the Siemens Healthineers IVD kit reagents/wash solutions.

Table 4-5 sets out the estimated value of the foregone returns that would arise due to downstream users having to replace the analysers rather than invest in other equipment or capital. These losses are significant from a public health perspective given that this is a diversion of funds from other public health investments.

Table 4-5: Foregone returns from premature replacement of analysers relevant to Applied for Uses #1 and #2 (PV @ 3.5%)

Type of analyser	No affected Range: 50 – 200	Expected lifetime Range: 5 – 20	Average remaining life – 2021 Range: 0 - 10	Average price (£ 2021) Range: £25,000 – 75,000	Average foregone returns due to premature investment in new analysers Range: 10,000 – 30,000	Total foregone returns due to premature investment in new analysers (2022) Range: £0.5 – 10 million
Use #1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	# D, E
Use #2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total						[redacted]

However, the capital costs of replacing the analysers together with the value of foregone returns would not be the most significant impact on their current users, as discussed further below.

Other costs associated with the premature replacement of Siemens Healthineers analysers

Validation costs: as mentioned above, there will be a transition period when switching from one platform to another. The new analyser would need to be tested, test results will need to be verified and, in some cases, new benchmark values (values against which tests results are measured) would have to be established. This process usually takes 12+ months but may be possible to complete in 10-12 months under significant time pressure. To carry out the validation, both staff and IVD kits and accessories will be needed to carry out the tests. The number of person hours needed during 10-12 months period is difficult to estimate due to the variation in time needed per test and the level of automation. Each analyser offers a range of assays that can be tested; some or all of them could be of interest to any one customer and for each of the assays of interest additional kits would need to be purchased for the needs of validation tests. The material cost of validation is not quantified here as it is deemed to be only marginal, compared to the cost of replacing the analysers themselves.

Other tendering costs: clearly, several employees would need to be involved in the tendering process. The labour cost for their involvement is not quantified here.

Lost profits: Siemens Healthineers' customers who engage in commercial activities will lose profit for the duration of the validation period. It has not been possible to acquire the information necessary to calculate the lost profits for these actors, but it is expected to be a substantial financial burden for the actors in questions.

Potential outsourcing costs: if the new analyser is not acquired early enough to complete the necessary validation testing before the Sunset Date, Siemens Healthineers customers might need to outsource or cease the testing during the verification period. This cost cannot be quantified (but see further below a discussion on the likely increase in test costs when testing is outsourced).

Impacts on workflow: while the Siemens Healthineers analysers can be placed alongside competitor analysers, laboratories tend to prefer consolidation to one analyser/supplier if possible, to improve workflow efficiency. As such, having to introduce new, potentially non-Siemens Healthineers analysers to their operations can be anticipated to affect the workflow of the customers.

Impacts on research: some of Siemens Healthineers' customers, such as research centres and universities, carry out research using the current analysers and IVD kit reagents/wash solutions. If there are ongoing studies using the current platform, they would likely have to restart the studies as the data would change. These delays will lead to costs like additional labour and testing materials, but it has not been possible to estimate these costs.

Impacts on patients: any gap in the ability of hospitals in particular to undertake clinical tests may have a significant impact on patient outcomes, and the ability of health care services to undertake timely diagnosis and care.

Availability of Alternative 3

Use #1 & Use #2

Currently, the Siemens Healthineers portfolio does not include alternative analyser platforms which provide the same diagnostic tests and do not have some reliance on OPE-containing IVD kits and/ or wash solutions.

In terms of competitor platforms, there are analysers available which offer similar diagnostic tests (with some exceptions), however it is unknown whether these are OPE-free. If a customer chose to move to a different platform, presumably the requirement for the analyser to be OPE-free would be a specification of the tendering process and customers would be able to ascertain that this was the case before proceeding.

It should be noted that it is the Siemens Healthineers plan to ensure that all the current platforms become OPE-free as per the REACH Response Plan presented in this AoA-SEA document; however, it will take time to achieve this across the full range of platforms/analysers/IVD products due to the complexities discussed in Section 4.1.

Hazard and risk of Alternative 3

Use #1 & Use #2

Given that any alternative platform or analyser that a customer could potentially purchase under this scenario is not known as it would depend on their specific needs, and that any platform would likely use a range of alternative detergents across the range of IVD products available on any selected analyser, it is not possible to fully evaluate the hazard profile of this alternative scenario.

However, any customer moving to a new platform would presumably ensure that it was OPE-free, and thus we can assume that OPEs would no longer be used by those customers if this scenario was

implemented. It is worth noting however that IVD kit reagents and IVD wash solutions contain other chemicals, normally in very low concentrations and volumes, and it is not possible to ascertain what these would be in any alternative platform that the customer purchased until the tendering process commenced.

Conclusions on Alternative 3

Use #1 & Use #2

While this alternative would mean significant costs and delays (up to 2 years) during which time tests could not be performed and therefore healthcare providers and patients would not receive diagnostic results. It is likely the only viable option that Siemens' downstream customers in the public health sector would have if they wanted to continue to perform diagnostic testing in the longer term.

4.3.4 Alternative 4: Outsourcing of the tests that depend on OPE-containing IVD products to a third party

This scenario explores the potential alternative of out-sourcing all the diagnostic tests performed by the IVD products within the scope of this AfA to a third party. Potentially this could mean outsourcing to reference laboratories outside the UK in the case where only OPE-containing IVD products were available on the UK market for certain tests, or in the case where there was insufficient testing capacity within the UK.

Substance ID, properties, and availability

Not relevant for this alternative.

Technical feasibility of Alternative 4

Use #1 & Use #2

Outsourcing of certain diagnostic tests is known to be a short-term action plan for customers (where possible) when for various reasons, individual tests are not available for a short period of time. To do this, customers would typically take the following steps:

1. Identify reference laboratories which are able to perform the diagnostic tests necessary, preferably in the near vicinity due to the time-sensitivity of certain tests and potential degradation of patient samples.

2. Define requirements and specifications, e.g. type of tests, reference ranges, turnaround times, etc., then request quotations, potentially from a number of laboratories to ensure competitive costs.

3. Agree costs; larger laboratories will normally then need to add a supplier to an approved supplier list, which typically requires an exchange of paperwork confirming that the laboratory has the necessary documentation, accreditations, insurance policies, etc.

4. Make receipt and delivery arrangements for the laboratory to accept samples from the healthcare provider, or via the contracting laboratory.

5. Receive and process results, then following usual protocol to issue test results to healthcare providers.

Following the steps above takes additional time and incurs significant additional costs compared to normal testing, which will be discussed further in the economic feasibility section.

To consider specifically the scenario whereby customers were no longer supplied with any of the OPE-containing IVD products in the Siemens Healthineers portfolio, the above process would need to be followed by numerous customers and for a large range of products, particularly in the case of larger customers. The time involved in doing this would be significant, with the likelihood that just one laboratory, if they had OPE-free technology, would not be able to accommodate the exact same range of tests the contracting laboratory was looking for. Therefore, more than one, possibly multiple external laboratories, would need to be used, thus compounding the work involved in following the steps outlined above.

In the immediate aftermath of a refused Authorisation, in the case of emergency testing, e.g. those tests that require a 1-hour turnaround to support emergency care would initially have to stop while the above steps were followed. If it became necessary to send certain tests out of the UK for processing, emergency tests could not be performed due to the time it would take to export samples and obtain results.

Sending samples outside the UK could be technically feasible for non-emergency samples that are stable during storage. Still, any transport activity would extend the time needed for a diagnostic result and contradict the high level of standardisation and automation of IVD applications that are designed to test a large number of samples in a short time for a broad range of diagnostic parameters. Furthermore, transport across national borders might also cause complications regarding legal aspects (e.g. transport of infectious materials).

Since it is not feasible for a large laboratory to outsource all testing sending out samples for certain tests would also in many cases require that additional samples are drawn from the patient. Typically, several parameters are tested in the same sample. If all these parameters are run on the same analyser, or on different analysers in the same lab, all tests can be done from the same sample tube. However, if some of the tests are sourced out, additional samples tubes are required. While this may not be a problem in many cases, there are certain types of samples (e.g. paediatric samples, CSF samples) where it would be very hard to obtain additional sample volume.

In addition, where an IVD wash solution is affected, all tests that are performed on the analyser are affected. In such cases the number of tests impacted would be much higher and would increase the efforts required to find a suitable set of laboratories to outsource the diagnostic testing to. In such cases, it could be an option to switch to a laboratory in the EEA (as the closest locations) where Authorisation has been granted.

Overall, outsourcing might be an option only for (a) customers with small number of affected tests which do not require instant results and have or can establish a business relationship with a larger reference laboratory, and/or (b) a limited period, as a temporary solution. In the context of this analysis outsourcing is considered as a possibility only if OPE-free technology is available within the UK. The realism of outsourcing the testing to third party laboratories outside the UK (i.e. in the EEA)

is questionable, as, arguably, the results of tests would be obtained with delay and at an increased cost to cover collection and transport to the non-UK diagnostic testing facility.

Economic feasibility and economic impacts of Alternative 4

Use #1 & Use #2

There is insufficient information available to allow the quantification of the cost of outsourcing. The patterns and cost of outsourcing of testing during the period of transitioning to new analysers are likely to vary between customers:

- It can be assumed that particularly in the case of large customers who currently use several of the impacted Siemens Healthineers analysers, outsourcing would make operations costlier. Firstly, if outsourcing was a cheaper option, it would may been put in place already by Siemens Healthineers' customers (if time delays did not give rise to issues). Secondly, a 2007 paper by US-based researchers indicated that reference laboratory testing comprised only 1.6% of total testing volume in 2006, while contributing a disproportionate percentage of total laboratory cost (19.5%) (Ardisson, Iafrate and Lewandrowski, 2007). Where many samples are required to be tested on a daily basis, the cost of outsourcing as a long-term solution would be prohibitive;

- On the other hand, outsourcing might reduce costs in specific cases, for example, where the Siemens Healthineers customer is using an analyser for only a few specific assays and for only few tests per year. It might be cheaper for a reference laboratory to run these tests as they could benefit from economies of scale.

Overall, the cost of outsourcing cannot be monetised. However, given the poor technical feasibility and availability of this alternative, this alternative would be unlikely to be implemented in a context other than a temporary solution until a new analyser is purchased to replace an existing Siemens Healthineers analyser.

Availability of Alternative 4

Use #1 & Use #2

For some diagnosis activities it is not unusual to send patient samples to specialised laboratories. Such laboratories exist and are used. Outsourcing has the advantage that no trained staff, analysers and consumables have to be available. Therefore, such an approach might fit a practice many healthcare institutions perform anyway.

Nevertheless, it is our assessment that there would not be sufficient capacity within the healthcare system to outsource all OPE-relevant diagnostic tests performed with Siemens Healthineers IVD products to alternative laboratories within the UK where OPE-free alternative tests are available. In the case where tests had to be sent out of the UK, again it is our assessment that capacity "at speed" would ultimately be an issue, even if the cost and turnaround impact were to be ignored.

Hazard and risk of Alternative 4

Use #1 & Use #2

In the case where diagnostic activities were outsourced, the global hazard profile of the use would not be reduced. We can assume that although the risk from releases of OPEs would be reduced within the UK, it would remain outside the UK.

In the case where alternative OPE-free diagnostic tests could be identified on the UK market, the environmental risks arising from the use of OPEs within the two Applied for Uses would be eliminated. However, a full hazard assessment cannot be made on the range of potential alternatives as it is not known if alternative OPE-free products are available across all of the impacted tests, or what detergents are used in such applications where they are available (although several of the detergents already on the market have less hazardous properties than OPEs based on their known classifications).

Conclusions on Alternative 4

Use #1 & Use #2

Given the huge additional capacity that would be required within the UK healthcare system to absorb the thousands of daily diagnostic tests carried out using the Siemens Healthineers IVD products falling within the scope of this AfA, this is not considered to be a feasible alternative for customers. Customer surveys that Siemens Healthineers conducted of larger customers have also confirmed this view. Write-ups of consultations with two large UK hospitals are given in Appendix 1 to this document.

Outsourcing within the UK also relies on OPE-free IVD kits performing the same diagnostic tests being available in every case, and it is Siemens Healthineers' understanding that this is not the case. Where only OPE-dependent alternative tests exist, outsourcing outside the UK would need to occur, with long turnaround times and additional trans-frontier shipment requirements making this an infeasible option.

4.3.5 Alternative 5: Cessation of diagnostic operations which involve the use of OPE-containing IVD products

This alternative explores the possibility of hundreds of customers across the UK ceasing their OPE-relevant operations within the UK healthcare system.

Substance ID, properties, and availability

Not relevant for this alternative.

Technical feasibility of Alternative 5

Introduction

While there are no technical reasons as such why a laboratory could not stop diagnostic testing, clearly the impact to the healthcare system would be significant and it would be unacceptable to stop supplying healthcare providers and patients in the UK with potentially life-changing or life-

saving test results. Many customers will also have contractual obligations to supply diagnostic test results to various healthcare providers. Technical considerations are described below for each of the Applied for Uses.

Use #1

If a customer was no longer able to use any OPE-containing IVD kit reagent, they would be forced to discontinue the associated diagnostic testing and thus could not provide results to healthcare providers. All other available IVD kits available for the analyser system (i.e. those for other diagnostic tests and which do not contain OPEs) could still be used, therefore this alternative would not result in a complete loss of the diagnostic capacity that is performed on an affected analyser owned by the customer. Nevertheless, the range of testing could be significantly reduced.

Use #2

If a customer was no longer able to use an OPE-containing IVD wash solution for an analyser, none of the IVD kits available for that analyser could be used. This would lead to a complete loss of the use of that analyser as each IVD wash solution is analyser-specific and has been tested and approved for use with all IVD kits available for that analyser. This is regardless of whether those IVD kits themselves contain or depend on OPEs or not. The # D analysers would be impacted .
Customers that currently operate such analysers, often a multiple number in the case of larger laboratories, could not perform any diagnostic testing using these analysers.

Economic feasibility and economic impacts of Alternative 5

Use #1 & Use #2

The effect on UK healthcare systems from ceasing the diagnostic tests performed with the IVD kit reagents and wash solutions that fall within the scope of the Applied for Uses would be devastating from a social (but also political) perspective. Economic costs would extend far beyond any profit losses of commercial laboratories or cost savings of laboratories who would abandon their Siemens Healthineers analysers. The real cost would include the increased burden of undiagnosed disease and the associated impact of increased morbidity and mortality.

The impacted IVD products cover a very wide range of assays and, whilst monetisation of the economic impact is not possible, it should be clear that the cost of this alternative to society would be extreme. As a result, customers' healthcare systems would do their utmost to avoid this scenario. As indicated earlier, the IVD kits falling within the scope of Use #1 are associated with an estimated # B,D (range: 1-10 million) diagnostic tests in the UK in 2021; for IVD kits depending on the Use #2 wash solutions, the respective number of diagnostic tests in 2021 is estimated at # B,D (10 -20 million). Over the requested review periods, this would equate to # B,D million (range: 30 – 40 million) and # B,D million (range: 40 – 50 million) tests respectively for the two uses.

Availability of Alternative 5

Use #1 & Use #2

Since many of the OPE-containing IVD kit reagents and IVD wash solutions are used in the testing of serious but also common diseases like e.g. cancer, heart disease, hepatitis, etc. it would simply not be an available option for customers to discontinue diagnostic testing. These are vital diagnostic testing services that could not simply be stopped, with the result being a significant deterioration in the healthcare system. Other options would have to be explored by customers to ensure the continuation of testing.

Hazard and risk of Alternative 5

Hazards to the environment arising from the use of OPE would be completely eliminated.

Conclusions on Alternative 5

Use #1 & Use #2

It is not a realistic option to stop diagnostic testing across the vast range of the IVD products falling within scope of this AfA. Diagnostic testing must continue to ensure healthcare providers and their patients receive results which are often life-changing or life-saving. Every other available avenue would be explored by customers to ensure the continuation of testing.

Some larger hospital institutions analyse more than one million samples in their diagnostic laboratories per year and often function as a regional diagnostic centre. As a result, no or only limited diagnostic capacities could be experienced on a regional scale if the IVD products in scope of this AfA were no longer available.

4.4 Most likely "Non-use" Scenario

Based on the analysis presented above, the most likely "Non-use" Scenario would be based on Alternative 3, i.e. the purchase of new analysers that only use OPE-free IVD kit reagents or IVD wash solutions, provided such analysers utilising OPE-free wash solutions and with a sufficient number of types of OPE-free IVD kit reagents were available on the market. The justification for this is:

- Alternatives 1, 2 and 4 are not known to be available, certainly not to cover the vast range of affected IVD products; and

- Alternative 5 would result in the cessation of diagnostic services to healthcare providers across the UK and would be accompanied by significant social costs which would far outweigh the environmental impact from the continued use of OPE-containing IVD products in the EEA.

Alternative 3 is also considered the least costly option and lends itself to (at least partial) monetisation of the economic impacts of non-Authorisation.

As previously explained, the assumptions made are overly optimistic. Given how widespread the use of OPEs in the IVD industry is, and the different ranges of assays catered for by different analysers on the market, most DUs would likely end up with a mix of new analysers, outsourcing of tests and

reduction of diagnostic capabilities with unforeseen and potential extreme consequences on healthcare systems and patients.

5 Impacts of Granting Authorisation

5.1 Economic impacts – benefits of continued use

5.1.1 Introduction

Under the "Non-use" Scenario, customers of Siemens Healthineers would not be allowed to continue using OPE-containing IVD products placed on the UK market. The key (over-optimistic) assumption is that customers would switch to alternative analyses and third-party IVD products thus affecting sales of IVD kit reagents and wash solutions manufactured by a variety of actors within and outside the UK (Siemens Marburg, Siemens Healthineers facilities in the USA as well as OEMs).

It should be noted that several of the IVD kit reagents, the use of which is covered by Applied for Use #1 are manufactured in Marburg, Germany and are covered by a granted EU REACH Authorisation.

The full range of impacts that would be avoided if an Authorisation was granted and which will be presented below can be summarised as follows).

Table 5-1: Overview of (direct) economic benefits for the Siemens Healthineers supply chain under the "Applied for Use" Scenario

Impacted stakeholder	Use #1	Use #2
Customers of Siemens Healthineers	Continued access to a range of IVD kits reagents that contain OPEs and which will allow full functionality for a wide range of analyser platforms, most notably: [redacted] # D,E table	Continued ability to operate [redacted] analysers which depend on the use of OPE-containing wash solutions
Siemens Marburg	Profits from sale of OPE-containing IVD products Authorised under EU REACH in the EEA would be preserved	Profits from sale of [redacted] OPE-containing IVD wash solutions would be preserved. Profits from sales of kits used on analysers using the wash solutions which are dependent on the continued use of OPE-containing IVD wash solution) in the UK would be preserved
Siemens Healthineers facilities in the USA and Japan	Profits from sale of OPE-containing kits made in the USA would be preserved	Profits from sale of OPE-containing kits used in the UK on analysers that depend on OPE-containing IVD wash solutions [redacted] would be preserved
OEM suppliers of IVD products distributed by EDC in Duisburg	Profits from sales of numerous OPE-containing IVD kit reagents to Siemens Healthineers would be preserved	Profits from sales of OPE-containing IVD wash solutions to Siemens Healthineers would be preserved
Suppliers to Siemens Marburg	Profit associated with sales of products and services to Siemens Marburg associated with this "Applied for Use" would be preserved	Profit associated with sales of products and services to Siemens Marburg associated with this "Applied for Use" would be preserved

Table 5-1: Overview of (direct) economic benefits for the Siemens Healthineers supply chain under the "Applied for Use" Scenario		
Impacted stakeholder	**Use #1**	**Use #2**
Healthcare systems and patients	Continued/uninterrupted access to wide range of diagnostic assays	Continued/uninterrupted access to wide range of diagnostic assays

The chosen "Non-use" Scenario is Alternative 3, i.e. the purchase of new analysers that only use OPE-free IVD kit reagents or IVD wash solutions, and forms the basis for the calculations of benefits and costs to society from granting an authorisation. The main assessment periods used are the requested review period of 12 years for both Use #1 and Use #2 (although it is expected that Use #2 will be phased out within 5 years).

5.1.2 Economic impacts for Siemens Healthineers customers

Use #1

Avoided cost of premature replacement of analysers

As described in Section 4.3.3, under the "Non-use" Scenario # D,E (range: 50-250) existing (2021 stock, # D,E by end 2022) analysers would need to be replaced prematurely in the case of Use #1. The economic costs for the existing 2021 stock are # D,E million in lost residual value and # D,E million in foregone returns due to the inability to invest in other equipment/projects yielding a positive return (range: £5 – 25 million).

Other avoided costs

As described in Section 4.3.3, the continued use of OPE-containing kit reagents would allow customers of Siemens Healthineers to avoid a range of additional costs such as:

- Validation costs;
- Other tendering costs;
- Lost profits (for commercial laboratories);
- Potential outsourcing costs;
- Impacts on workflow;
- Impacts on research (where relevant); and
- Impacts on the ability to undertake diagnostic tests and to ensure patient care.

It has not been possible to quantify and monetise these costs.

Use #2

Avoided cost of premature replacement of analysers

As described in Section 4.3.3, under the "Non-use" Scenario # D,E (range: 50-200) existing (2021 stock, # D,E by end 2022) analysers would need to be replaced prematurely for Use #2. The economic costs for the existing 2021 stock are # D,E million in lost residual value and # D,E million in foregone returns due to the inability to invest in other equipment/projects yielding a positive return (range: £1 – 5 million).

Other avoided costs

The additional costs described for Use #1 above would also apply here. It has not been possible to quantify and monetise these costs.

Important note

The above estimates are an underestimate of the benefits accruing for customers from the continued use of OPE-containing IVD products. The estimates are based on very optimistic assumptions that OPE-free technology/analysers are available on the EEA market and that a switch to a third-party platform would occur much more seamlessly than past experience suggests. Switching to an alternative analyser typically takes 6-24 months to implement. The practical and economic implications of such a long downtime period are largely ignored in this analysis but would have a profound adverse effect on the delivery of diagnostic testing under the "Non-use" Scenario.

As such, the benefits shown above should be seen as reflecting the minimum impacts.

5.1.3 Economic impacts for other Siemens Healthineers operations in the UK

Use #1

Sales of IVD kit reagents

As shown in **Table 3-3**, the present value of profits made by Siemens Healthineers from sales of OPE-containing IVD kit reagents to UK-based customers over the period 2022-2032 (inclusive) is estimated at ca. £# D,E (range: £25-100 million). This profit would be preserved if the continued use of those kits by downstream users was authorised. It is important to recognise that these kit reagents are used across 27 different analysers/systems, as summarised in Table 2-2.

A significant portion of these sales are linked to EEA-made kits (i.e. kits made by Siemens Marburg or EEA-based OEMs), which were recently granted a EU REACH Authorisation (Use #4 in the Siemens Marburg Authorisation).

Use #2

Sales of IVD wash solutions

As also shown in Table 3-5, the present value of profits made by Siemens Healthineers from sales of OPE-containing IVD wash solutions to UK-based customers over the period 2021-2032 is # D,E (range: €100k - 5 million). These wash solutions are specific to the # D,E and to the kits used on this platform. If these wash solutions could no longer be used, then it would no longer be possible to undertake the range of # D,E diagnostic tests that can be run across this platform. The relevant analysers would no longer be functional. As noted above, this would equate to some # D,E million tests over the requested 4 year review period.

In addition to sales of the OPE containing wash solutions, sales of non-OPE containing kit reagents would also be affected if the Use #2 wash solutions could no longer be used. This is because the use of these kit reagents relies on the use of the wash solutions between tests. As detailed above, the PV value of the profits associated with these sales over the requested 4 year review period is # D,E

million (range: 1-5 million), taking into account the reduction in use in the was solutions over the period. Economic Impacts for consumers/patients.

Under the "Non-use" scenario, the patients relying on tests provided by Siemens Healthineers' customers may experience economic losses due to increased costs of testing e.g. from increased testing costs for Siemens Healthineers' direct customers, hospitals, commercial laboratories or other. However, this price increase would simply be a transfer of the costs from Siemens Healthineers' customers to the patient. This means that it is a distributional affect rather than an additional costs to society.

5.2 Human Health or Environmental Impact – Costs and benefits of continued use

5.2.1 Environmental benefits

Under the "Non-use" Scenario, the environmental impacts described in Section 3.3 would be avoided. The CSR describes exposure scenarios under which releases to the aquatic environment and sludge occur after Triton™ X-100/Triton™ X-405-containing wastewater is treated in municipal STPs and 53% of the sludge is sent to agricultural soil or compost.

Table 3-9 and **Table 3-10** presented the estimated annual and daily releases of 4-tert-OP over the requested review period for each of the Applied for Uses. Annual aquatic + sludge releases of 4-tert-OP in the year 2022 are projected to be ca. # H (range: 10-100) and # H (range: 100-1,000) kg/y for Use #1 and #2 respectively. For Use #1, annual emissions will decrease steadily until 2033 when use will ceases. For Use #2, annual emissions will decline more significantly over the requested review period until the wash solutions are phased out by the end of 2025. The total amount of 4-tert-OP released by DUs over the requested review periods is projected to be # H (range: 100-500) kg for Use #1 and # H (range: 100-500) kg for Use #2, bringing the total to # H (range: 100-500) kg. This is split between aquatic and sludge releases with a ratio of # H. It must be understood however that these releases reflect the use of # C,D diagnostic tests carried out on Siemens Healthineers analysers across the UK.

Environmental 4-tert-OP concentrations calculated for the local scenarios due to the wide dispersive Use #1 are below the EQS for risk characterisation; they are also below the EQS for Use #2 but to a lesser degree, although these solutions will also be phased out in # F. As a result, and PECs for all compartments will dramatically decline. # H,J Thus, adverse effects for water and sediment organisms are less probable than in the local scenario. The assumptions made in the CSR are generally conservative. Therefore, average concentrations are expected to be lower than those indicated in the local assessment.

In any case, risks for the local and the regional environment cannot be excluded; the EQS values cannot be considered no effect concentrations. Endocrine effects on aquatic and sediment organisms at even lower concentrations cannot be excluded. Since 4-tert-OP bound to sludge may enter agricultural soils, it may also pose a risk to terrestrial organisms. Concentrations calculated for this compartment are, however, considerably below the latest research value.

Overall, the benefit to the local environment from non-Authorisation would be low and will be outweighed by the associated the socio-economic impacts.

Over the requested review periods, the releases translate to the following:

- Quantities per diagnostic test:
  - Use #1: # H, J kg per test; (range: 1E-06 - 5E-06kg)
  - Use #2: # H, J -06 kg per test (range: 4E-06 – 8E-06kg)

- £ / kg released:
  - Use #1: # J (range: £0.5 – 1 million)
  - Use #2: # J (range: £1 – 50K)

5.2.2 Health benefits for affected patients

The number of IVD kits sold in the UK in 2021 represented approximately:

- Use #1: ca. # C, D kits (range: 10,000 – 50,000); and
- Use #2: ca. # C, D kits (range: 1,000 – 10,000) associated with the use of OPE-containing wash solutions.

Each kit may deliver hundreds or even thousands of different tests. For example, the # D uric acid has # D tests/kit (range: 1,000-10,000), while some of the other # D IVD kits have # D (range: 10,000-100,000) tests/kit.

Siemens Healthineers is able to translate the number of IVD kits sold to the equivalent number of diagnostic tests performed with those kits. Thus, it can be estimated that in 2021, DUs in the UK may have performed ca. # D million (range: 1 -10 million) tests using IVD kits within the scope of Use #1. The number of tests conducted alongside the wash solutions of Use #2 was ca. # D million (range: 10 -25 million).

The IVD kits in question provide results used in the diagnosis of a multitude of diseases and conditions of which only a modest sample is presented in **Table 5-2** and includes tests for the detection and/or monitoring of:

D

[redacted]

- [redacted]

Ultimately Siemens Healthineers' customers are using the impacted IVD kits at around # C, D, E healthcare provision locations across the UK for delivering to patients test results which can be life-saving or life-changing. These kits can detect severe abnormalities that affect pregnancies, can support the early diagnosis of certain cancers, bone diseases, blood abnormalities and other conditions some of which are untreatable (e.g. end stage renal disease). The # D test (entry #14 in the table below), for instance, is one of the 30 most important, most ordered and highly established parameters to be tested. Any disruption to the supply of these kits should be measured not only monetarily from a healthcare provider perspective but also in terms of the impact to patients' lives and outcomes. Patients who cannot undergo vital tests within the required timeframe will be significantly adversely affected; this is one of the reasons the IVD industry is so strictly regulated, to ensure healthcare providers can rely on the performance and supply of products, including the delivery of timely results.

Table 5-2: Disease information relating to diagnostics carried out by OPE-containing kits placed on the EEA market by the Siemens Healthineers European Distribution Centre

#	Diagnostic field	IVD kit name	Intended use
1	[redacted]	[redacted]	[redacted] # D table [redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]

Table 5-2: Disease information relating to diagnostics carried out by OPE-containing kits placed on the EEA market by the Siemens Healthineers European Distribution Centre			
#	Diagnostic field	IVD kit name	Intended use
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

Table 5-2: Disease information relating to diagnostics carried out by OPE-containing kits placed on the EEA market by the Siemens Healthineers European Distribution Centre			
#	Diagnostic field	IVD kit name	Intended use
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
Source: Siemens Healthineers Document Library (https://doclib.healthcare.siemens.com/home?forceLogin=true)			

5.3 Social impacts

5.3.1 Avoided job losses for Siemens Healthineers' customers

Siemens Healthineers' customers are diverse, and the impacts would likely vary. In a commercial lab or large hospitals that have staff dedicated to diagnostic testing it may be the case that a reduction in the product portfolio would make some staff redundant for a period of time. It is, however, unlikely that there will be a substantial number of jobs lost amongst Siemens Healthineers' customers due to a reduction in the portfolio. In any case, quantifying and monetising such impacts is not possible.

5.3.2 Avoided job losses for Siemens Healthineers

Avoided job losses at the European Distribution Centre (EDC)

In case of non-Authorisation, the volume of IVD products distributed by the Duisburg-based EDC to the UK would decrease and this could have a small impact on jobs at the facility. Siemens Marburg estimates that the impacted products under Uses #1 and #2 at the EEA level combined account for # D % (range: 1-10%) of the overall volume distributed annually. Using this percentage as an indication of the FTEs that might be lost if an Authorisation was not granted for the two Applied for Uses under UK REACH suggests that at most # E (range: 1-10) FTEs at the Duisburg EDC could be lost that could be attributed to a decision related to UK REACH Authorisation. As a result, such impacts are not considered further here.

Avoided job losses at Siemens Marburg

Both Use #1 and Use #2 are linked to operations at Siemens Marburg, Germany. It is uncertain how many workers would potentially lose their jobs due to the refused Authorisation of these two uses in the UK, given that Authorisation has been granted under EU REACH for these two uses and for the use of OPEs in the manufacture of the kits. As a result, such impacts are not considered further here.

Avoided job losses in the UK linked to the supply chain

The analysers and IVD reagents/wash solutions are not produced in the UK, so there is no direct employment in the UK in their manufacture. There are ~500 jobs located in the UK linked to the Siemens' supply chain for these diagnostic products for servicing and managing sales, [redacted] # E

5.4 Wider economic impacts

5.4.1 Trade competition

Overview

A key parameter of the above analysis is that customers of Siemens Healthineers in the UK would have to abandon their Siemens Healthineers analysers in the event of non-Authorisation (particularly for Applied for Use #2). As Siemens Healthineers cannot be certain what alternative technologies might be available on the market, a (perhaps overly optimistic) assumption has been made that such OPE-free technology would be available to customers on the Sunset Date. In reality, for each of the impacted IVD kits and wash solutions placed on the UK market by Siemens Healthineers there is, at the time of applying for Authorisation, no way of conclusively determining which competitor products that may be 'equivalent' to each of the Siemens Healthineers IVD products do or do not contain OPEs, as this is Confidential Business Information for the manufacturers involved.

Competition

Siemens Healthineers is aware that some of its competitors will be submitting AfAs for their own uses of OPEs. It can also be safely assumed that competitors are actively looking into reformulating their products without OPE. Siemens Marburg has researched the market for third-party IVD kits that cover the same assays to establish whether OPE is mentioned as component of the kit reagent in the respective Safety Data Sheets. These searches have generated information (see **Table 4-3**) that can only be considered a snapshot of the situation at the end of 2021 and does not reflect any contemporaneous efforts that Siemens Healthineers' competitors may be making towards the reformulation of their IVD kits or indeed the UK Authorisation of their continued use of OPEs. This table cannot be seen as all-encompassing and is only used here as a limited example to underpin the arguments made.

The table presents the findings of searches for selected IVD kits that fall within the scope of the present AfA. It can be seen that for some kits, third-party replacements would also contain OPEs. Such kits would normally need to be used on third-party analysers; they usually could not be used as drop-in replacements on Siemens Healthineers analyser platforms.

The key assumption made for the "Non-use" Scenario is that Siemens Healthineers' competitors would be able to supply analysers which do not depend on OPE and cover the same/similar range of assays as the Siemens Healthineers impacted analysers and, as such, that customers would move to those third-party analysers. This is the only reasonable assumption that could be made in order to assume that disruption to the provision of diagnostic services across the UK could be realistically (but also socially and politically) acceptable. This would decrease Siemens Healthineers' market share while benefitting competitors and could well cause imbalances to UK competition, depending on which competitor is able to replace the Siemens Healthineers analysers [redacted]. If, theoretically speaking, the [redacted] was the only company able to substitute the Siemens analysers, its market share could well exceed 50% in the UK and could become by far the dominant player in the market.

Again, as it is not possible to know to what extent competitors are dependent on OPEs, whether their products cover all relevant Siemens Healthineers assays, what the competitors UK Authorisation and reformulation plans are and how successful their Authorisations will be, it is not possible to predict changes to competition in the UK market under the "Non-use" Scenario.

5.4.2 Changes to international trade and re-location of economic activity

As per the discussion above, it is not possible to express an informed view as to whether changes to international trade would be significant. This will depend on the availability of OPE-free technologies post 2022.

5.5 Distributional impacts

The following table summarises the envisaged distributional impacts from the granting of an Authorisation.

Table 5-3: Distributional impacts from the continued use of OPE in the Applied for Use #1 & #2		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
UK-based customers of Siemens Healthineers	Access to #D, E, H, J (TAble (range: 50 – 150) IVD products and # E (range: 1-5) wash solutions allowing important assays to be run on up to 27 different analyser systems would be lost. In total, ca (range: 100-400) analysers would also no longer be viable and would have to be prematurely replaced at an estimated cost of million (range: £5 - £25 million) in foregone returns and lost residual value. Customers would also incur significant validation, tendering, workflow and other impacts due to the premature replacement of current analysers.	Low local releases of 4-tert-OP to the aquatic environment and sludge after treatment of wastewater at municipal STPs. Overall aquatic release of 4-tert-OP in the period 2022-2033 is estimated at ca. # H (range: 100-500) kg; overall release of 4-tert-OP to sludge in the period 2021-2040 is estimated at ca. # H (range: 10-100) kg
Applicant: Siemens Llanberis on behalf of Siemens Marburg and Siemens Healthineers more generally	Continued manufacture and sales of Use #1 IVD kits to UK-based customers– profits made from Triton™ X-100/Triton™ X-405-dependent IVD kits: £ # E (range: £40 – 50 million) (PV, 2021-2032, 3.5%). Continued manufacture and sales of Use #2 wash solutions at a profit of £ # E (range: £0.5 – 1 million) (PV, 2021-2025, 3.5%). Continued sales of OPE-free kit reagents reliant upon the use of the was solutions at a profit of £ # E million (range: £1 – 10 million) (PV, 2021-2025, 3.5%)	Low local releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP
OEMs	OEMs can retain the markets for the IVD kit reagents that they formulate with OPE within the UK. Profit margins are not known	Low local releases of OPE to the environment
Siemens' UK supply chain	Potential job losses within the Siemens UK supply chain responsible for sales and servicing of kits and analysers	As above
Public (patients) in the UK	Cost of tests will not increase (if outsourcing of tests is avoided)	Continued access to the full range of testing capabilities of hospitals and labs thus allowing quick test results, diagnoses and treatments for a range of diseases. An estimated combined # J million (range: 10 - 100 million) tests can continue to be carried out over the period 2022 to 2033 inclusive across Use #1 and Use #2
		OPE releases for Use #1 estimated at # H,J kg per test. OPE releases for Use #2 estimated at # H,J kg per test.

6 Conclusions

6.1 Comparison of the benefits and risk

Table 6-1 summarises the socio-economic benefits of continued use of Triton™ X-100 and Triton™ X-405 by Siemens Healthineers' customers that were presented in Section 5. Overall, a benefit of £ # E million and £ # E million (Present Value, @ 3.5%) (range: £2 – 80 million) can be estimated for the Applied for Uses #1 and #2 respectively. These are associated with total releases over the requested 12 and 4 year review periods of # H (range: 10-100kg) and # H kg (range: 100-400kg) of 4-tert-OP respectively, from the use of kit reagents and wash solutions delivering # H and # H million (range: 20 – 80 million) diagnostic tests.

It should be appreciated that the cost of non-Authorisation could be much greater due to: a likely 'domino 'effect on Siemens Healthineers' sales for both the relevant IVD products; the additional costs that Siemens' customers would face when being forced to prematurely retire their existing analysers and move to new systems; and the impacts on patient diagnoses and care during such a transition period:

UK-based customers using the impacted products would abandon their Siemens Healthineers analysers due to the loss of the full functionality they had been purchased for

↓

Customers would incur increased costs due to the need for premature replacement of analysers and due to the foregone returns from displacement of expenditure on other equipment or projects

↓

Fewer active analysers would mean that sales of OPE-independent kits would be heavily impacted

↓

Loss of use of the wash solutions would impact on the ability to use non-OPE-based test kits, which run on systems that require the use of the wash solutions

↓

Manufacture of IVD kit reagents and products for the retired analysers would stop cease

↓

The ability of Siemens customers to undertake current levels of diagnostic testing across a range of health concerns would be impacted, leading to reductions in patient diagnoses

↓

Patient care outcomes in the UK could be significantly affected due to delays in diagnoses or a an inability to undertake tests whiles new systems are acquired and implemented

Table 6-1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario				
Stakeholder affected/impacted	**Description of impact**	**Quantification of impact**		**Considered in the total monetised benefit calculated below**
		Use #1 (2021-2033)	**Use #2 (2021-2025)**	
Benefits to the applicant and/or their supply chain				
UK-based Siemens Healthineers customers	Continued operation of existing (and future) Siemens Healthineers analysers that use the affected IVD kits and wash solutions – avoided cost of premature replacement of analysers - Use 1: # D analysers (2021 stock) - Use 2: # ED analysers (2021 stock)	# E (2021 prices)	# E (2021 prices)	Yes
	Avoidance of cost increases from outsourcing diagnostic tests	Not quantified	Not quantified	No
EDC Duisburg, Siemens Marburg and Siemens Healthineers	Uninterrupted/unaffected manufacture, sale and distribution of OPE-dependent kits and wash solutions to UK customers – Gross profit to be made	# E (PV 2021, 3.5%)	# E (PV 2021, 3.5%)	Yes
	Uninterrupted/unaffected manufacture and sale of IVD kits the use of which depends on the continued availability of OPE-containing wash solutions	N/A	# E (PV 2021, 3.5%) sales of all non-OPE IVD kits	Yes
Benefits to other actors				
Healthcare providers/patients	Continued access to tests needed for the diagnosis and treatment of a range of diseases/conditions	Ability to carry out # H million diagnostic tests linked to Use #1, enabling patient diagnoses across a range of disease endpoints		No – no quantified data
		Ability to carry out # H million diagnostic tests linked to non-OPE based kit reagents due to availability of the Use #2 wash solutions from		No – no quantified data
Overall Aggregated socio-economic benefit of continued use of OPE		# E **(range: €10-100 million)**	# E **(range: €1-10 million)**	

On the other hand, the total emissions of OPE to the environment under the "Applied for Use" Scenarios were shown in **Tables 3-9** and **Table 3-10**. The benefits and releases per Applied for Use over the requested review period are shown in **Table 6-2**.

Table 6-2: Cost of non-use per kg, per test and per year			
Use #1			
Parameter	**Present Value, 2021-2033**	**Number of tests, 2021-2033**	**Annualised value (average over 12 year period)**
Total cost of non-use	[redacted]	[redacted] # E, H, J table [redacted]	[redacted]
Total emissions	[redacted]	[redacted]	[redacted]
Ratio	**£[redacted] per kg (range: £100k – 2.5 million per kg)**	**[redacted] kg per test (0.5-5 mg/test)**	**£[redacted] per kg (range: £100k – 2.5 million per kg)**
Use #2			
Parameter	**Present Value, 2021-2025**	**Number of tests, 2021-2025**	**Annualised value (average over 5 year period)**
Total cost of non-use	[redacted]	[redacted]	[redacted]
Total emissions	[redacted]	[redacted]	[redacted]
Ratio	**[redacted] per kg (range: £10k – 100k per kg)**	**[redacted] kg per test (0.5-10 mg/test)**	**£[redacted] per kg (range: £10k – 100k per kg)**

The ratio of the total cost of non-Authorisation (i.e. the benefit of continued use) and the total emission of 4-tert-OP to the environment is **£[redacted] # E, J to £[redacted] # E, J per kg of 4-tert-OP released for Use #1 and Use #2 respectively.**

It must be recognised that these figures are significant underestimates. While the impacts on Siemens Healthineers and customers in terms of the costs of new analysers have been monetised, the additional impacts on health services and patients have not. The potential magnitude of these latter impacts is reflected in the number of tests that could no longer be carried out, with these directly reflecting on the potential for patient diagnoses at hospitals and other medical practices. On a per test basis, the releases are at the level of [redacted] # J [redacted] and [redacted] #J [redacted] kg per test, or [redacted] # J [redacted] and [redacted] # J [redacted] milligrams of 4-tert-OP released per test.

6.2 Information for the length of the review period

6.2.1 Introduction

In a 2013 document, the ECHA Committees outlined the criteria and considerations which could lead to a recommendation of a long review period (12 years) (ECHA, 2013):

1. The applicant's investment cycle is demonstrably very long (i.e. the production is capital intensive) making it technically and economically meaningful to substitute only when a major investment or refurbishment takes place.

2. The costs of using the alternatives are very high and very unlikely to change in the next decade as technical progress (as demonstrated in the application) is unlikely to bring any change. For example, this could be the case where a substance is used in very low tonnages for an essential use and the costs for developing an alternative are not justified by the commercial value.

3. The applicant can demonstrate that research and development efforts already made, or just started, did not lead to the development of an alternative that could be available within the normal review period.

4. The possible alternatives would require specific legislative measures under the relevant legislative area in order to ensure safety of use (including acquiring the necessary certificates for using the alternative).

5. The remaining risks are low and the socio-economic benefits are high, and there is clear evidence that this situation is not likely to change in the next decade.

The requested review periods for the continued use of OPE by EEA-based customers of Siemens Healthineers are:

- Use #1 – End use of IVD kit reagents: 12 years; and
- Use #2 – End use of IVD wash solutions: 5 years from sunset (January 4th, 2021)

6.2.2 Criterion 1: Siemens Healthineers' investment cycle

Use #1

The full Siemens Healthineers product portfolio placed on the EEA and UK market is heavily impacted by the inclusion of OPEs on the REACH Authorisation list, with over [redacted] (range: 100-1,000) individual IVD products falling within the scope of REACH Authorisation which requires significant investment in resources and funds [redacted]. It is important to note that the successful substitution of Triton™ X-100/Triton™ X-405[10] in one product by a 'safer' alternative substance will not necessarily mean that this alternative will be appropriate as a substitute for the next product, even within the same product-line. The properties which make OPE effective in one product may be completely different to what makes it effective in another, and this is only proven through 'trial and error' feasibility testing.

As a result, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a Substitution Plan (described in Section 6.3). As part of this plan, all products which are connected to the [redacted] analysers (e.g. [redacted]) or which are expected to have a longer life-cycle ([redacted]) are being given the

[10] Use of Triton™ X-705 in the affected products will stop by the end of 2020.

highest priority in terms of Design Change, and plans to reformulate these products are underway on a per product basis.

Section 6.3 presents the different projects being conducted as part of the Substitution Plan which can be summarised as follows. Each project includes several formulations and finished products.

Table 6-3: Overview of Product Change and Design Change Projects under the Substitution Plan		
Parameter	**Use #1**	**Use #2**
Product Change Projects by Siemens Healthineers	[redacted]	[redacted]
Product Change Projects by OEMs	[redacted]	[redacted]
Design Change Projects by Siemens Healthineers	# F, G table	[redacted]
Design Change Projects by OEMs	[redacted]	[redacted]
End-of-Life Projects by Siemens Healthineers	[redacted]	[redacted]
End-of-Life Projects by OEMs	[redacted]	[redacted]
Total	[redacted]	[redacted]

In other words, there are expected to be:

- # F, G bullets Design Change Projects for the relevant IVD kit reagents that fall under Applied for Use #1;
- [redacted] Product Change Projects for IVD kit reagents that fall under Applied for Use #1; and
- [redacted] End-of-Life 'projects' (where some IVD kit reagents will not be reformulated as the relevant analyser product lines are coming to the end of their life soon).

Table 6-3 demonstrates that this will have to be a joint and co-ordinated effort between Siemens Healthineers (with its teams in Marburg and in the USA being involved) and several OEMs.

The key driver behind the request for a 12-year review period for Use #1 by Siemens Healthineers' customers hinges upon the need for a period of continued use of OPE that would allow the planned Design Change Projects for the # D IVD kit reagents (which are necessary to the [redacted] # D analysers) to be completed. In total, there will be 4 projects involving # G kits (Projects # # G) which will involve # G (range: 10-100) IVD products/formulations and will have a combined resource requirement of [redacted] # G (range: 50-100) FTE. These cannot be undertaken simultaneously and whilst overlaps exist, the final project (Project # G) will need to run until 2032 inclusive.

Therefore, a 12-year review period will allow the roll-out of the significant investment in R&D that Siemens Healthineers is planning for the Design Changes to be implemented.

Use #2

For the wash solutions falling within the scope of Applied for Use 2, Section 6.3 presents (and **Table 6-3** summarises):

- 1 Design Change project for the # D, G business line.

In the original EU application this use included 5 wash solutions, now only 2 remain due to extensive re-design work. The total resource input was 10 FTEs for the projects.

6.2.3 Criterion 2: Cost of using alternatives

Siemens Healthineers is in the process of re-designing numerous OPE-dependent IVD products across all of its affected product lines and the estimated cost of reformulation is # E (range: €10-100 million) for the Design Change effort alone, not including R&D resource. This investment in OPE substitution activities diverts significant funds and efforts away from other areas of the Siemens Healthineers business # D.

There is a key point here: alternatives for the users of OPEs under the presently Applied for Uses are different to the alternatives for Siemens Healthineers. For the former, alternative kits and/or analysers would be the theoretical replacement for OPE-containing IVD products, while for Siemens Healthineers (and relevant OEMs) alternative substances (or combinations thereof) would be the key replacements for the OPEs themselves.

With regard to the cost of alternatives for Siemens Healthineers' customers, as discussed in Section 4.2, most alternatives to the use of OPE-containing IVD products are infeasible, either because they are unavailable or because they would lead to severe disruption/cessation of the provision of diagnostic services at many healthcare provision locations across the EEA. The one alternative option which may to a certain degree be feasible is the replacement of the Siemens Healthineers analysers by third-party analysers that do not rely on the use of OPEs. Even in that case, disruption to the provision of diagnostic service should be expected, as switching from one analyser to another typically requires preparation that lasts 6-24 months.

As shown in **Table 4-4**, premature replacement of Siemens Healthineers analysers would impact ca. # D (range: 100-1,000) analysers which are relevant to Applied for Uses #1 and #2.

The overall present value cost of the premature replacement of Siemens Healthineers analysers is amounts to ca. £ # E (range: £10-25 million, 2021 prices). If the two Applied for Uses are seen in isolation, this cost would be allocated to each of them, due to the heavy overlap between the Applied for Uses (essentially, analysers may use both OPE-containing kit reagents and OPE-containing wash solutions).

These costs do not include other important costs which have not been possible to quantify such as:

- New analyser validation costs;
- Tendering costs;
- Lost profits (for commercial testing laboratories);
- Potential outsourcing costs;
- Impacts on workflow; and
- Impacts on research activities.

It is therefore clear that the use of alternatives on the Sunset Date and in the absence of an Authorisation for the continued use OPEs would impose significant costs and operational constraints both to the downstream users of OPEs and the applicant (and the wider Siemens Healthineers organisation and their OEMs).

6.2.4 Criteria 3: Results of R&D on alternatives and availability of alternatives over the longer term

As previously explained, the customers of Siemens Healthineers are not in the IVD product manufacturing business and would not be able to research any alternatives to OPE-containing IVD products. The availability of direct alternatives for Applied for Uses #1 and #2 (i.e. third-party analysers that do not depend on OPEs) is currently unclear as Siemens Healthineers do not have knowledge of the competitors' use of and dependence on OPEs now and in the future.

In terms of substitution of OPEs within Siemens Healthineers' IVD products, Siemens Healthineers has been undertaking R&D on potential alternatives and Section 4.1.1 describes relevant experiments that have been conducted. To establish the most appropriate alternative substances for all the impacted IVD kits and wash solutions would require resources and time. For commercial OPE-containing products or those that have obtained final design status, only select feasibility testing has been conducted by Siemens Healthineers. The strategy has been to determine the efforts required to identify potential alternatives to Triton™ X-100/Triton™ X-405 in several critical assays spanning several different technologies. While there are examples of this being completed successfully using # F, there are also examples where it has been demonstrated that # F is not an acceptable replacement.

Each assay product's design is unique and each one must be fully tested to confirm that the selected alternative is acceptable. There are no guarantees of success at the outset of this process, even if an alternative substance has been successfully (or unsuccessfully) proven for a similar assay. Therefore, physico-chemical properties and toxicological classification of potential alternatives are only aids in prioritising the order in which alternatives are evaluated. This has been used in practice; however, due to the complex and unique nature of each milieu, as well as the potential multiple effects OPEs convey to IVD assay performance, there is no single alternative that has been shown to be a universal replacement. Differences among the IVD products arise from the different critical raw materials (i.e. antibodies, signal technology, etc.) which manifest unique biological and physiochemical characteristic to the products. As such, each product behaves in a different way and has different performance characteristics. The reason for this appears to be based on molecular interactions between the chemicals and the proteins involved, but the exact mechanisms are not fully understood. Each product is therefore produced by following a unique and product-specific protocol.

The efforts undertaken as part of the extensive work done by the Siemens Healthineers organisation to identify alternative substances continually benefit future efforts. Consequently, after careful consideration of the above parameters, it is concluded that several alternatives, alone or in combination, must be experimentally evaluated on a 'per product' basis to successfully implement alternatives across the impacted Siemens Healthineers portfolio.

The challenges in identifying suitable alternative reagents for each and every impacted IVD product (less those that have been decided to be progressively retired) are reflected in the timeframe of Siemens Healthineers' Substitution Plan which is described in more detail below. The reformulation of the # D IVD kit reagents is driving the timeline for substitution for Applied for Use #1 due to the # D important kits that need to be reformulated (by 2033) while the reformulation of the very important # D wash solution is driving the overall timeframe for substitution for Applied for Use #2 (by 2025). Given the

need for undertaking R&D for each IVD product separately, these timeframes cannot realistically be shortened within the limitations of Siemens Healthineers' own resources.

Indeed Siemens Healthineers has already speeded up its efforts in this regard, with this resulting in a shortening of the original requested review periods in this application for Authorisation from 2040 to 2033 for Use #1 and from 2032 to 2025 for Use #2 which were sought under EU REACH.

6.2.5 Criterion 4: Legislative measures for alternatives

In relation to alternatives for customers, the installation of a replacement analyser requires its validation. In practice, there is a transition period when switching from one platform to another. The new analyser would need to be tested, tests results will need to be verified and, in some cases, new benchmark values (values against which tests results are measured) would have to be established. This process usually takes 6-24 months.

On the other hand, with regard to alternatives for OPEs themselves, after the reformulation of the IVD kits to substitute away from OPE, the performance of the products would have to be verified and any performance changes will require a re-registration in most countries.

Generally, the process of preparing an application for re-registration of an IVD kit and submitting it to the relevant authorities would include the following steps:

1. Change Project initiated by the Siemens Healthineers change team;
2. Initial Regulatory Assessment prepared by RA;
3. A Product Change Notification sent to all Country RA representatives to inform them of the change and request feedback on registration impact and supporting document needs;
4. The Product Change Notification feedback would be consolidated and provided back to change team to incorporate requirements into project planning;
5. RA would review the change verification plans and reports and would prepare and collect the requested documentation to support country re-registrations. The Regulatory Assessment would be updated based on the verification results and the Country RA feedback; and
6. Country RA would prepare the applications to be submitted to their regulatory Authority. Q&A between Country RA and Business line RA would follow as needed to generate the required submission content.

Siemens Healthineers would typically allow # D months for submission preparation in each country. There are about 80 countries with re-registration requirements and submission requirements to each country vary. Siemens Healthineers estimates that re-registrations would generally be required in ca. 50 countries. This estimate is based on the fact that about 80 countries have regulatory requirements and 31 are under the EU + EFTA. The review time in the different countries vary between a few months to three-and-a-half years, with China taking the longest (42 months). The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market.

Siemens Healthineers' REACH Response Plan, presented in Section 6.3, takes into account the regulatory activities that would be required after the completion of the reformulation activities.

The OPE Authorisation/Sunset Date under EU REACH coincides largely with the timeline for implementation of the new IVD Regulation 2017/746. Under the current legislation (IVD Directive 98/79/EC), the vast majority of the products are self-declared and can be brought into the market without involvement of a notified body. This will change dramatically under the new IVD Regulation when about 80% of the products will fall under the responsibility of a notified body. Prior to the date of application of the IVDR (May 2022) most IVD companies will be working to full capacity in nearly all departments implementing the new IVD regulation and preparing dossiers for the IVDR registration. Likewise, the notified bodies in each country will be dealing with large numbers of IVDR registrations. Working on the OPE replacement in parallel to the IVD Regulation re-registration could jeopardise the latter, and thereby the placing on the market in the EU (and in many other countries requiring a CE-mark).

6.2.6 Criterion 5: Comparison of socio-economic benefits and risks to the environment and effective control of the remaining risks

Benefit-cost ratios for Applied for Uses

The benefit-cost ratios for the continued use of OPE under Applied for Uses #1 and #2 as presented above are significant underestimates of the actual benefits conferred by the continued use of OPEs in the Applied for Uses as they only encompass benefits that could be readily quantified and monetised. The true benefit-cost ratios must be assumed to also encompass:

- The significant benefits to the health of numerous patients across the EEA who are diagnosed with or monitored for a wider range of diseases through the use of millions of tests that contain OPEs and which are placed on the market by Siemens Marburg. It is estimated that 30.7 million tests were performed in the UK using IVD kits falling within the scope of Use #1 and ca. 42.7 million tests were performed alongside the IVD wash solutions of Use #2;

- The profits that manufacturers of OEM IVD products and analysers (those made on behalf of Siemens Healthineers and other, third-party ones) would be preserved;

- The profits for Siemens Healthineers from sales of IVD products and analysers that might potentially be indirectly impacted if the continued use of OPE-containing IVD products within the UK was not authorised and thus Siemens Healthineers would suffer loss of economies of scale and global reputational damage; and

- The significant cost, impacts on healthcare provision, operational disruption, inconvenience for a period of a minimum 6 months (but potentially as high as 24 months) which the users of Siemens Healthineers analysers would avoid, as they would avert the premature replacement of their units.

In addition, the monetised benefits that have been presented above have been discounted over time, whilst the physical quantities of 4-tert-OP released under the Applied for Uses have not.

Finally, under the "Non-use" Scenario it cannot be certain that there will be capacity for the relevant tests to be undertaken in the EEA, as it is expected that IVD kits of other manufacturers which may also perform these tests could also rely on OPEs or the capacity to perform the impacted tests could be limited.

Potential actions for further minimisation of the remaining risks

Appendix 2 (Section 10) presents an analysis of the appropriateness of existing Risk Management Measures that UK customers of Siemens Healthineers currently employ and the proportionality of additional measures that would be aimed at eliminating the releases of 4-tert-OP into the environment that arise from the continued use of OPE-containing IVD kit reagents and wash solutions.

The conclusions of the Appendix can be summarised as follows:

1. The current practice of discharging dilute diagnostic analyser wastewater to the public sewer system is in line with the EU regulatory framework for wastewater and waste management.

2. To segregate and ensure incineration of wastewater, customers would need to classify the wastewater not only as waste but specifically as 'hazardous waste' despite the fact it does not meet the criteria for classification as hazardous waste under the Waste Framework Directive.

3. Volumes of wastewater generated are very high in relation to the volume of OPEs used by customers.

4. There are environmental impacts from incinerating high volumes of wastewater to deal with relatively low volumes of OPE, estimates are provided in the Appendix.

5. There are some significant logistical challenges in separately collecting wastewater, particularly in certain cases, e.g. a large laboratory in an old building.

6. The costs of segregating the high volume of wastewater would be significant for healthcare providers, and bearing in mind that many customers are publicly-funded or 'not for profit' organisations. The Appendix indicates that one-off investments could cost thousands of Euros and the cost of incinerating the segregated wastewater would attract a typical cost of €1,000 per tonne. The Appendix demonstrates that large hospitals which handle considerable volumes of OPE as wash solution constituents and for which OPE concentrations in their diagnostic analyser wastewater are higher than other customers', could be faced with significant incineration costs. For large hospital 'hot spots' annual incineration cost of €0.5-1 million could be incurred.

Based on the above, it is considered that a move to segregation of wastewater for all customers would produce significant financial and logistical issues for a significant proportion of healthcare institutions in the UK. Minimisation of emissions via phase out of OPEs in IVD products a far more viable and cost-effective route.

Of relevance are the results of a survey of customers that Siemen Healthineers has undertaken. As discussed in Section 9.4.1, participants to the survey expressed concerns about the costs associated with changing their current wastewater management processes. The majority of those responding indicated the need for structural changes, increased costs, reliance upon external disposal contractors, need for increased storage, and the alteration of worker routines.

6.3 Substitution effort taken by the applicant if an authorisation is granted

6.3.1 Introduction to the process of substituting OPEs

There are three types of processes to be considered and described here when changing reagents, accessories (i.e. wash solutions) and processes (i.e. where OPE is a processing aid):

1. **Design Change Process (DCP)**: this is the type of project that will be initiated when it is planned to change the design of an existing product, or a formulation used in the manufacturing process needs to be changed.

2. **Product Development Process (PDP)**: this relates to the development and commercialisation of a new product; however, this also includes existing products where the reagent will be used on a new platform ([redacted]).

3. **Process Change**: this type of project will be initiated where an existing manufacturing process needs to be adapted. Process change refers to those changes where OPEs are only used during production but not in the final product. Therefore, the products subject to a process change are not in the scope of Uses #1 and #2 (but are relevant to Uses #1 of Siemens Marburg and Siemens Llanberis). Notably, products might be subject to both a process change and a PDP.

The typical duration of these projects is shown in two figures, **Figure 6-1** and **Figure 6-2**. The two figures show that, on average, a DCP or PDP could last up to 8 years, while a Process Change (presented below for completeness) could last 2-3 years. These average durations apply per group of IVD kits/wash solutions and it should be clear that for Siemens Healthineers several such projects would be required. The terms used in these two figures are explained in **Table 6-4**.

Table 6-4: Terms used in the description of activities encompassed in Siemens Healthineers' REACH Response Plan

Terms	Description
Feasibility Test	It includes comparison of "old" reagent with OPE and "new" reagent without OPE for key assay parameters (not all assay parameters are tested here, but the relevant ones). This is, where [redacted] In addition, this phase also includes stability testing to allow shelf life confirmation

Table 6-4: Terms used in the description of activities encompassed in Siemens Healthineers' REACH Response Plan	
Terms	**Description**
Design Change Phase	It includes verification [redacted], and report generation (RG) to close this phase.
[redacted]	[redacted]
[redacted] Preparation	It includes tasks such as [redacted] etc.
[redacted]	It includes [redacted]. The goal is to demonstrate no change in performance with the "new" reagent
Report Generation	Complete filing all necessary reports after [redacted]. This includes creating, reviewing and approving documents
Note-to-File	Prepare all necessary document to filing agency
[redacted] Activities	It includes preparing verification lot(s)/lot for sale, updating databases and infrastructure for design transfer/manufacturing activities, and filing all necessary documents. The dotted outlines indicate that the duration may vary
Close	File all necessary paperwork so that the product can be sold into the registered country

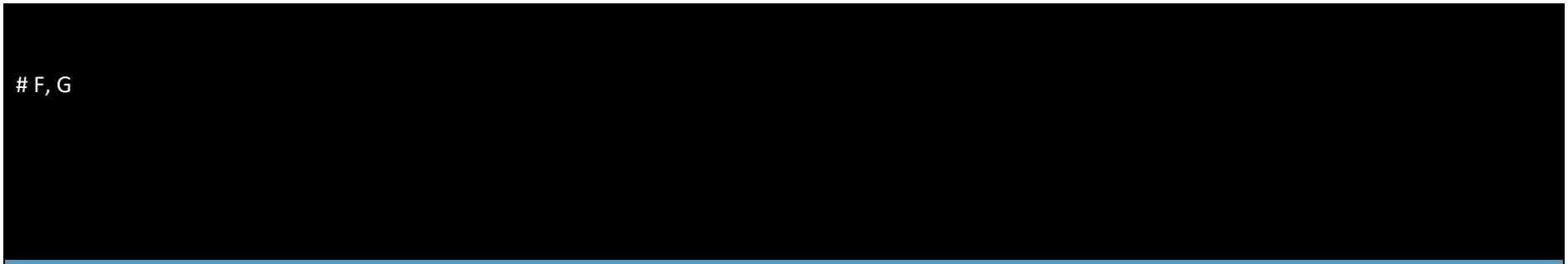


Figure 6-1: Overview of the duration of different types of substitution projects

6.3.2 OPE substitution strategy for Applied for Uses #1 and #2

Section 3 summarises the steps and durations involved in all projects involved in the phase out of OPEs in the two Applied for Uses. The key parameters of the projects involved are outlined for clarity in **Table 6-5**.

As previously explained, substitution of OPEs in IVD kit reagents can only happen on a product-by-product basis over time. The following guiding principles are the basis for Siemens Healthineers´ approach to eliminating OPEs from their portfolio over the coming years:

1. Siemens Healthineers' priorities in their active research activities to substitute OPEs are to focus first on IVD products that:
    a. are used often,
    b. are important for downstream users – that they serve key diagnostic parameters that are urgently needed to by customers and patients, and/or
    c. their substitution is economically feasible. Products in the portfolio for which new, replacement products are already in the pipeline will only be supported as long as customers really need them (see Point 3 below).

2. For some product lines there are already activities ongoing to introduce a follow up technology to the market [redacted]. Following the internal R&D policy not to develop new products that rely on OPEs (see Point 1 above), new OPE-free products will provide new alternatives for customers. Support for the "older" product lines will be limited to a period that gives the customer a reasonable time to switch to these new products. This mainly depends on investment cycles that determine the customer's potential to invest into new technology. Customers that have invested in a certain analyser platform must be given some time to have at least some benefit of its use. Thus, the phase out will be closely linked to the average time the analyser usually is used before replacement happens.

3. Each OEM supplier of IVD kit reagents that rely on OPE usually supplies only few products to Siemens Healthineers ([redacted]). These OEM suppliers have already started substitution/phase-out activities for these supplied products and for many substitution was accomplished by the Sunset Date. So, in the initial phase of a potentially granted Authorisation period, Siemens Healthineers will need to invest large parts of their research activities to requalify the IVD kits that rely on these OEM products. Thereby, Siemens Healthineers supports the substitution of OPEs in their own upstream supply chains and at the same time ensures that their customers can use the IVD kits that depend on OEM reagents/wash solutions without interruption.

4. Some products which are not requested very much by customers will be phased out after a reasonable time (this should be shorter than the phase out time for analysers and associated IVD kits).

Taking these principles into account the Substitution Plan presented in **Table 6-5** can be outlined per Applied for Use as follows:

- **Use #1**: there are two sub-sets of projects, one led by Siemens Marburg, the other led by Siemens Healthineers USA, in collaboration with OEMs, as appropriate:

  - *Marburg substitution projects*: Siemens Marburg will start with [redacted]. However, it should be remembered that Siemens Marburg will also be working on the elimination of OPE from the manufacturing processes of the IVD kits that fall under Applied for Use #1 (see separate AfA). Once the re-registration phase for these products starts, resources will be freed for the focus to shift to the [redacted] wash solution. The reformulation of the [redacted] wash solution must be done sequentially (as indicated in the REACH Response Plan) following the reformulation of the [redacted] IVD kit reagents. The reason for this is because the reformulated wash will need to be tested with all [redacted] assays ([redacted] products) used on the same platform (at the feasibility stage).

  - *Siemens Healthineers USA and OEM substitution projects*: the driving force behind substitution is the [redacted]. [redacted] formulations need to be reformulated and for reasons of resource and fund availability, this needs to be done gradually, over [redacted] projects starting in 2019 and finishing by 2033. This drives the overall timeline for reformulation work undertaken outside the EEA.

Use #2: The two wash solutions in scope will be reformulated or phased out by end 2025, with a year-on-year decrease in volume up to that point. Siemens Healthineers' focus on this extensive Substitution Plan does mean that significant funding and effort is diverted from other areas of the business and [redacted]

Table 6-5: Details of projects planned by Siemens Healthineers and OEMs for the phase out of OPEs in IVD products relevant to Applied for Uses #1 and #2

[redacted]

6.4 Links to other Authorisation activities under REACH

The discussion and analysis presented above should be seen in the context of other AfAs applied for Under EU REACH (and subsequently UK REACH) by Siemens Healthineers legal entities:

- Siemens Llanberis applied under EU REACH for its own continued use of OPE in the formulation and use of bead coating/washing solutions which are used in the manufacture of OPE-free # D IVD kits. This became an "in-flight" authorisation with the Final Opinion made by the Defra Secretary of State.

- Siemens Marburg applied under EU REACH for the continued use of OPE in the formulation of some of the OPE-containing IVD kit reagents and wash solutions (Uses #2 and #3) the end-use of which is covered by the presently Applied for Uses #1 and #2. The following dependencies are therefore are noted:

  - **EEA-based customers** relied on Siemens Marburg being granted an Authorisation for Applied for Uses #2 and #3 in order for OPE-containing IVD kit reagents and wash solutions to continue being manufactured in Marburg and then placed on the market;

  - **Siemens Marburg** relied on Uses #1 and #2 being granted an Authorisation in order for (a) EEA demand for the OPE-containing IVD kits manufactured under Applied for Use #2 to be maintained after the Sunset Date, (b) EEA demand for the OPE-containing IVD wash solutions manufactured under Applied for Use #3 to be maintained after the Sunset Date;

  - **Siemens Healthineers in the USA** relied on Uses #1 and #2 being granted an Authorisation in order for (a) EEA demand for the OPE-containing IVD kits manufactured in the USA and sold in the EEA market via the EDC to be maintained after the Sunset Date, (b) EEA demand for the OPE-containing IVD wash solutions manufactured in the USA and sold in the EEA market via the EDC to be maintained after the Sunset Date; and

  - **OEMs** manufacturing OPE-containing IVD kits and wash solutions which are subsequently sold by Siemens Marburg to EEA customers via the EDC relied on Uses #1 and #2 being granted an Authorisation in order for EEA demand for their OPE-containing IVD kits and wash solutions to be maintained after the Sunset Date.

7 References

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8 Justifications for confidentiality claims

[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	**Commercial Interest**	**Potential Harm**	**Limitation to Validity of Claim**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

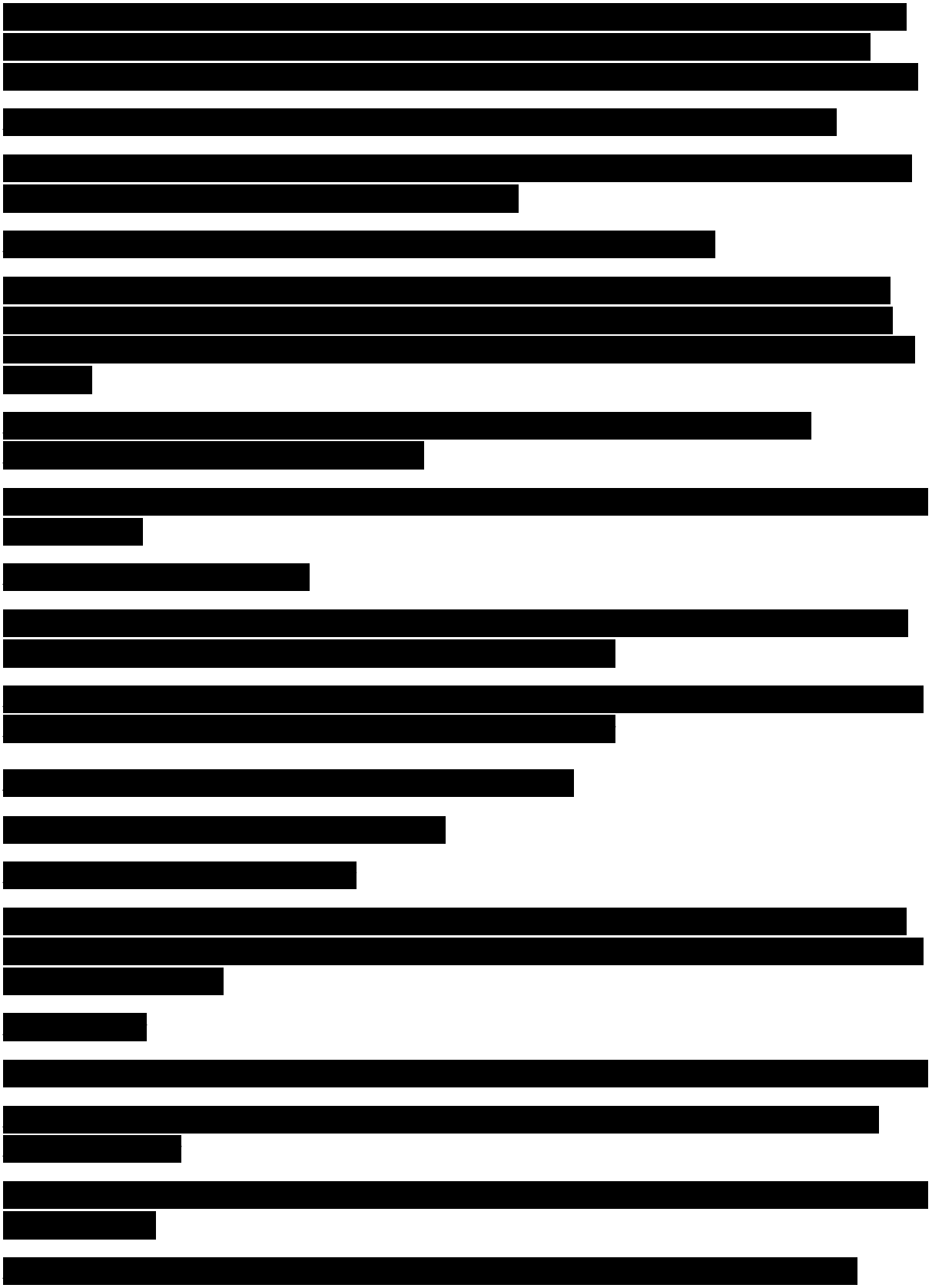
9 Appendix 1: Consultations

9.1 Introduction

Siemens Healthineers undertook two consultation campaigns. A short one where hospitals in the UK were sent detailed questions and representatives were interviewed on possible impacts from non-Authorisation as well as a much wider customer survey which aimed to encompass hundreds of customers on the possibilities of implementing additional RMMs for the control of releases of Triton™ X-100 arising from the use of Siemens Healthineers' IVD products in diagnostic activities. The following pages present copies of transcripts of interviews with the hospitals followed by a detailed analysis of the findings of the subsequent, wider survey of customers.

9.2 Interviews with selected customers

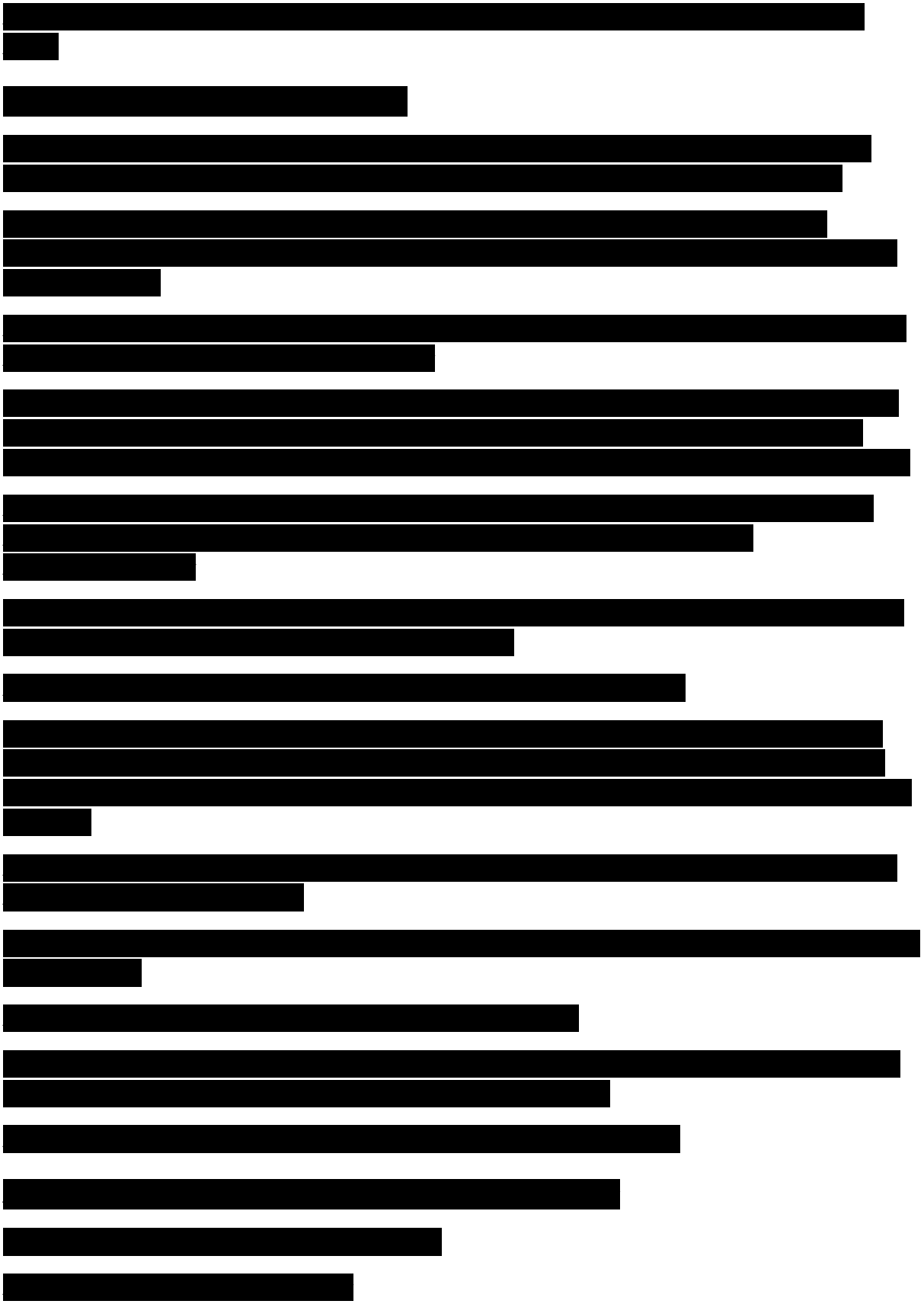
9.2.1 Interview with the # D, I entire Appendix 1



9.2.2 Interview with [redacted]

[redacted]

[redacted]



[redacted]

9.3 Downstream User survey methodology

To support the Siemens Marburg's AfA under EU REACH, a customer survey was undertaken with the aim of identifying potential impacts on customers as a result of authorisation. The survey was aimed at customers using OPEs. The survey, therefore, also set out to investigate the costs and impacts of introducing additional RMMs on customer businesses. The survey was designed by the independent third-party consultants-authors of the AoA-SEA document with the cooperation of Siemens Healthineers to ensure question relevance and comprehension of technical language. All questions were approved by Siemens Healthineers before the survey was launched.

A digital, web-based survey was deemed to be the most suitable approach. This was to provide respondents with fast, reliable, confidential and easy access to the survey, using the digital survey host *Survey Monkey*. The survey was made available and released in six languages (English, French, German, Italian, Spanish and Greek). These languages were selected to best represent Siemens Marburg's EU customer language requirements. An invitation to participate in the survey was sent via mail (using national postal systems and email) from Siemens Marburg to approximately [redacted] (range: 1,000-10,000) relevant EU companies on their customer database. The invitation provided a two-week window for responding. However, this was finally extended by another three weeks to allow for further response. The survey was launched in Week 3 of March 2019, to ensure the most up to date feedback possible from customers.

Regarding the sampling framework, the primary criterion was to identify only those companies which use Siemens Healthineers analysers and are end-users of OPE-containing products and also impacted by REACH Authorisation. It was therefore aimed at customers located within the EEA. No other criterion was used to pre-select companies invited to participate from the total Siemens Marburg customer database.

The survey contained 21 questions, including 6 which were related purely to demographic information (i.e. type of IVD facility, location (country and city/town), contact name, etc.), the number and model of Siemens Healthineers analysers and number of non-Siemens Healthineers analysers used. Particular attention was paid to [redacted] (range: 1-10) Siemens Healthineers analyser models of concern as these currently use the highest volume of OPEs. Questions also covered the handling processes of analyser wastewater, wastewater volume, costs associated with waste management, alternative processes for wastewater management, and customer perspectives on the tangible effects that separating analyser wastewater would have. Careful attention was paid to different models of Siemens Healthineers analysers, due to variation in OPE concentration in the products used on each type of analyser.

In designing the survey, both quantitative (typically closed) and qualitative (typically open) questions were included. Where quantitative data primarily provide input on the number and model of analyser, their volume and percentage of wastewater output, facility processes and costs associated with analyser use. A qualitative approach was used to gain more specific insights into the practical implications of collecting wastewater separately. Participants were invited to provide unlimited text input in response to this question, so as to provide a more comprehensive understanding of the issues.

The consultants follow a strict observance of GDPR rules and participant data was handled securely and confidentially. To ensure participants were able to 'opt out' of the survey, a link was included in the invitation/webpage which requested the participant to inform the consultants via email if they did not plan to participate in the survey. In acknowledgement of the unlikeliness of non-participants to respond via email due to the possibility of identification by email address, a clear and explicit GDPR statement on data confidentiality was visible on the webpage. The aim of reporting non-participation was to generate a metric that could potentially enhance the analytics of the survey results; however, no such notifications of non-participation were received.

In total, [redacted] (range: 10-200) responses to the consultation were received from customers in the UK. These responses are detailed and analysed in the sections below.

9.4 Survey summary report – UK

9.4.1 Survey response analysis (All responses)

Background

In 2017, [redacted] (range: 100-1,000) Siemens Healthineers customers located in the UK were invited to participate in the survey and [redacted] (range: 10-100) responses were received (all [redacted] (range: 10-100) responded to the English language survey; no English language responses from other countries), with most respondents based in England ([redacted]) (range: 10-100) [redacted]%) and a minority in Scotland ([redacted]) (range: 1-10) ([redacted]%); [redacted]% from towns and [redacted]% from cities. [redacted]% of respondents were happy to continue correspondence with the researcher to clarify their answers, whilst [redacted]% were not. And [redacted]% of respondents provided contact information, [redacted]% did not.

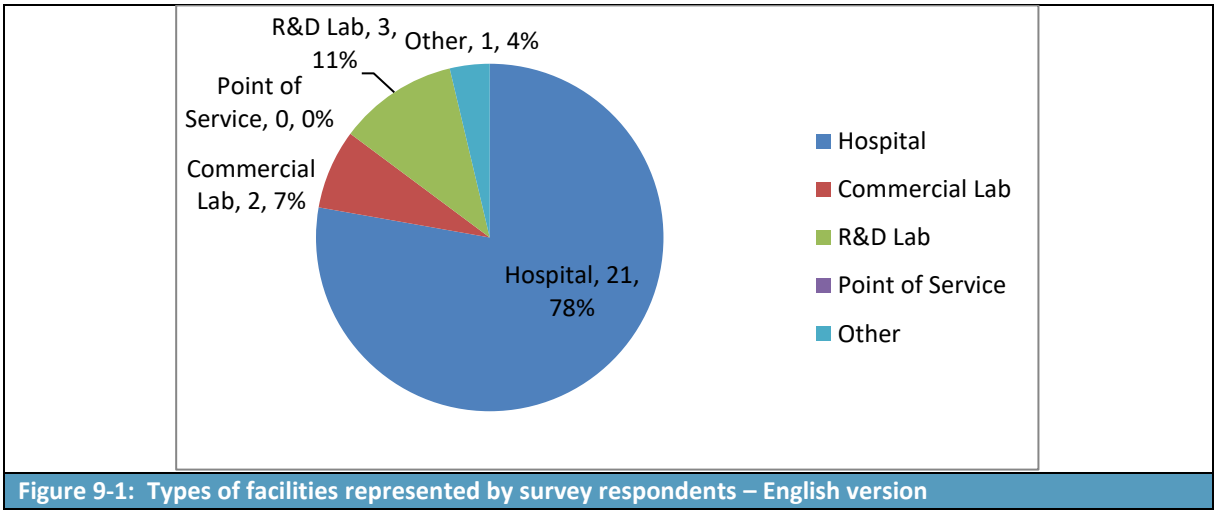


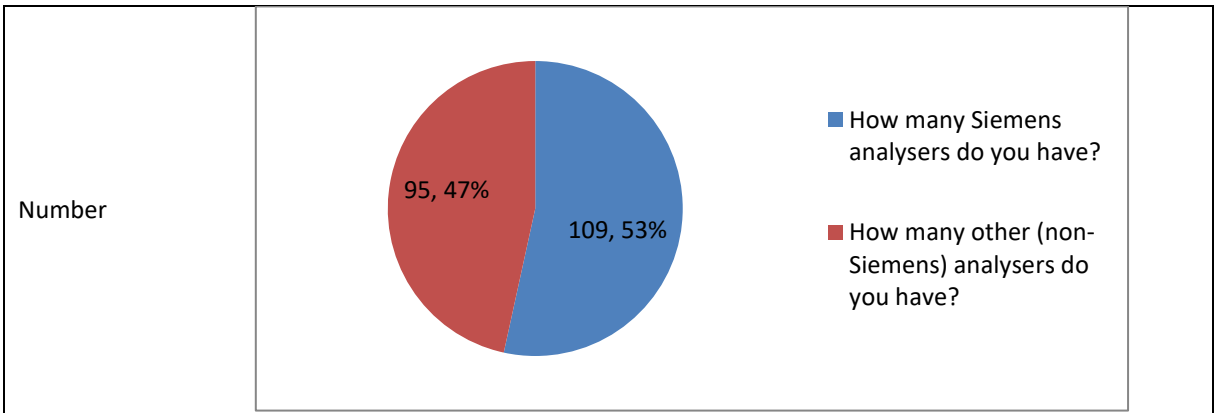
Figure 9-1: Types of facilities represented by survey respondents – English version

As **Figure 9-1** indicates, the majority of respondents represent Hospital laboratories. The total of [redacted] (range: 10-100) indicates that [redacted] (range: 1-10) respondent gave [redacted] (range: 1-10) answers to this question.

Number of analysers owned

Figure 9-2 below indicates use of Siemens Healthineers and non-Siemens Healthineers analysers. In total, this group of respondents uses almost as many non-Siemens Healthineers as Siemens Healthineers analysers [redacted] (range: 1-200), although [redacted]% did not provide an indication of ownership of any non-Siemens Healthineers analysers.

For [redacted]% of respondents, all analysers are located within [redacted] building. The remaining [redacted]% indicated an average of [redacted] (range: 1-10) sites.



Average owned per respondent

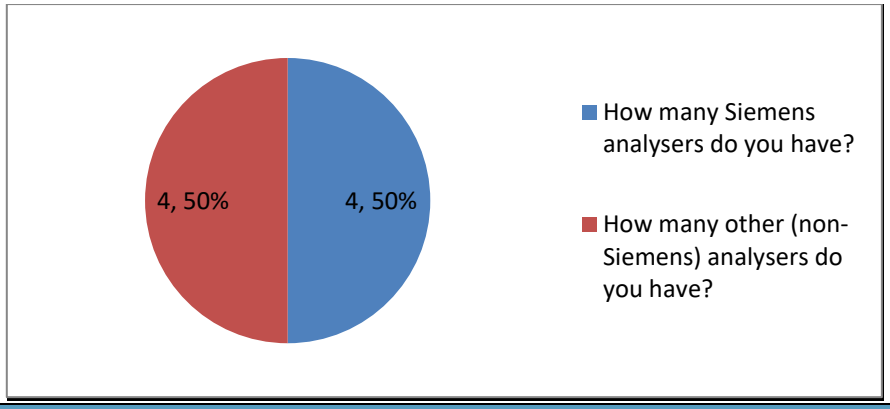


Figure 9-2: Number of Siemens Healthineers & other supplier analysers owned by respondents – English version

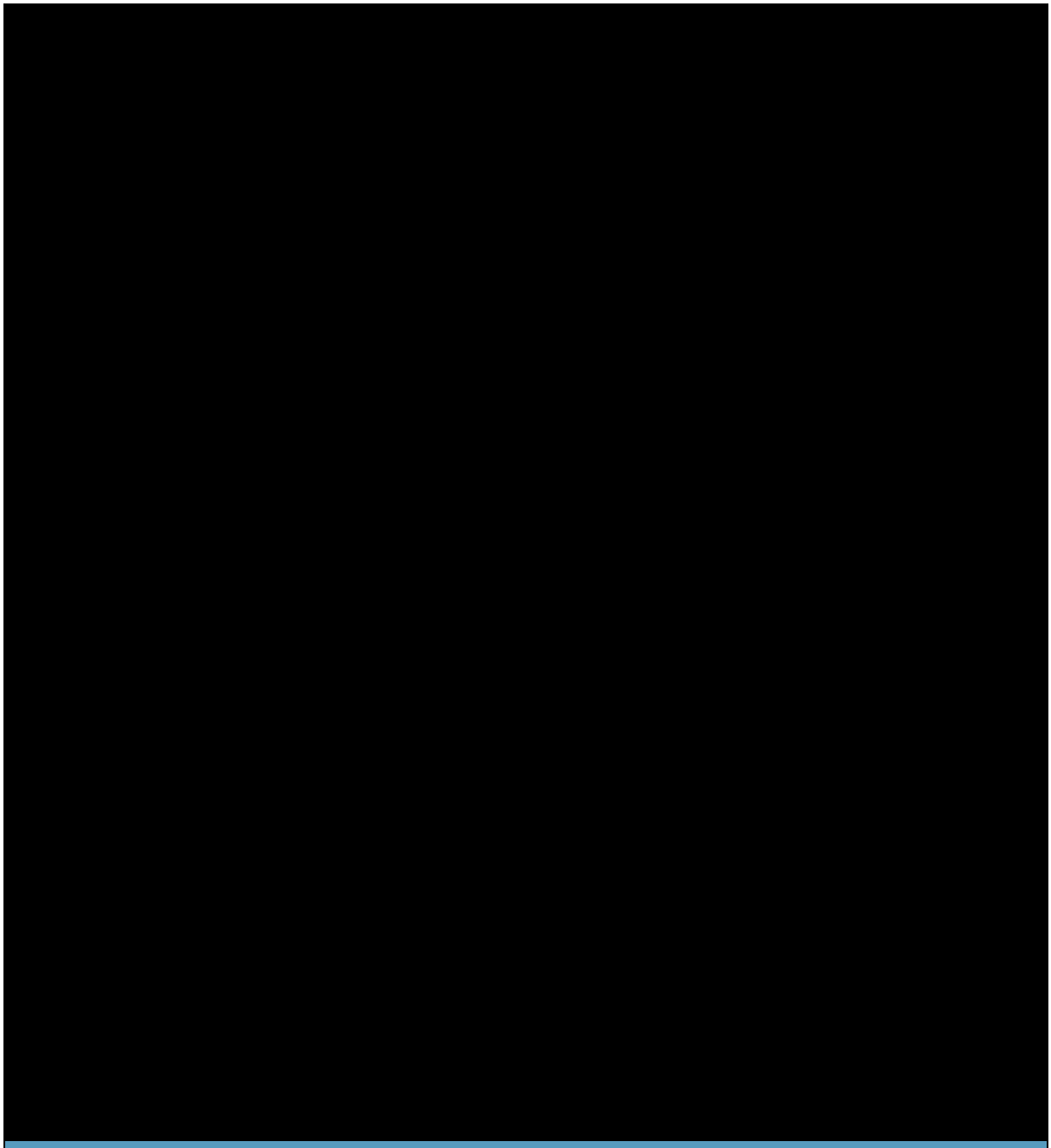


Figure 9-3: Number of respondents who own each Siemens Healthineers analyser model – English version

Table 9-1: Number of analysers owned by respondents – English version		
model	Total owned (Chemistry)	
Number of above models of all analysers	**(range: 10-100)** **(% of Siemens Healthineers analysers; % of total analysers)**	

Figure indicates which Siemens Healthineers models are *owned* by survey respondents; the table is not exhaustive but represents only how many respondents listed which Siemens Healthineers analysers. Comparatively, **Table 9-1** indicates the *number* of [redacted] analysers owned by the respondents. Respondents were asked to specify [redacted] analysers as these are known to use the highest volume of OPEs of all Siemens Healthineers analysers [redacted]. In total, [redacted] (range: 10-100) of the respondents' [redacted] (range: 100-1,000) Siemens Healthineers analysers were [redacted] models ([redacted]%). This result suggests that [redacted]% of all owned analysers (both Siemens Healthineers and non-Siemens Healthineers) were one of the referenced [redacted] models [redacted].

Processes for managing analyser wastewater

Table 9-2 outlines respondent processes for managing analyser wastewater. Some respondents use more than one method, or gave answers for both [redacted]% and [redacted]% of wastewater being collected in this way. As shown, the majority of processes include the disposal of wastewater directly to the drain ([redacted]% ([redacted]) (range: 10-100) indicated that over [redacted]% of their wastewater was disposed in this way). Considerably less frequently, wastewater is collected in a sump and manually emptied down the drain ([redacted]%). Regarding 'other' processes only [redacted] (range: 1-10) provided responses which can be generalised as collecting wastewater in containers, treating with Actichlor/caustic, and emptying via drains.

Table 9-2: Current handling of wastewater from Siemens Healthineers analysers – English version					
Responses	**Collected in a sump and manually emptied down the drain**	**Connected directly to the drain**	**Collected in a sump and disposed of as waste**	**Other**	**Total**
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of responses with more than [redacted]% of their waste disposed via this method	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of responses with less than [redacted]% of their waste disposed via this method	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Respondents were also asked to estimate the volume of wastewater their analysers generate annually. This question yielded low response rates ([redacted]) (range: 10-100), however, [redacted]% of those that did respond estimated [redacted] (range: 1,000 – 10,000) per annum ([redacted]) (range: 1-10).

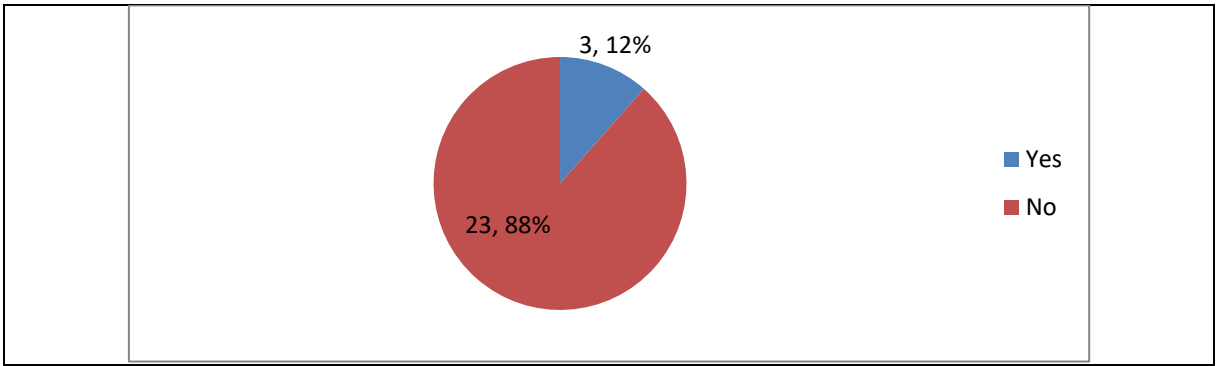


Figure 9-4: Survey question responses: "*Does your facility have access to a central waste collection system?*" – English version

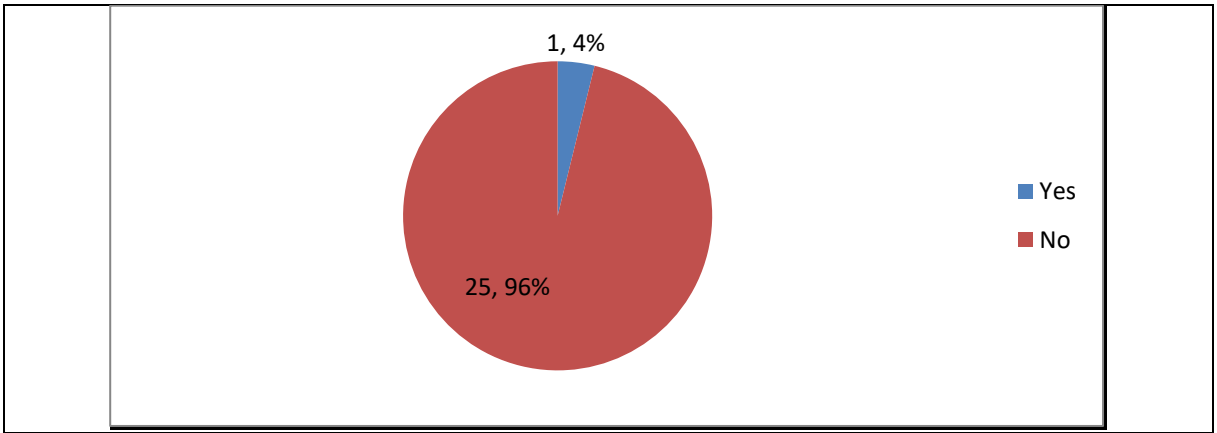


Figure 9-5: Survey question responses: "*Do you collect and send wastewater to a Wastewater Treatment Plant (WWTP) or Incinerator?*" – English version

Figure 9-4 indicates a strong tendency for respondents' facilities not to have access to central waste collection systems. Nor are they currently implementing special disposal of analyser wastewater via WTP or Incinerator (**Figure 9-5**). Of those that do collect and send wastewater for disposal, WWTP was the only method used. This suggests that for the majority of participants, alternative measures of disposal are not currently set up and it can be anticipated, as discussed in Appendix 3 (Section 11), that the associated costs for implementing this could be significant.

Estimates of technical and economic feasibility of additional Risk Management Measures

Participants were also asked to estimate the costs associated with their current wastewater management processes (collected in a sump and emptied down the drain, emptied directly down the drain, collected in a sump and disposed of as waste, other), as well as the costs associated with separating wastewater. Unfortunately, respondents did not provide any information that could be useful. Most respondents stated they "did not know" or simply provided no data.

Nevertheless, analysis of the qualitative responses indicated that respondents generally felt negatively about the potential costs associated with these changes. For example:

- [redacted]% of responses indicated that such changes would be accompanied by increased cost;

- [redacted]% noted the need for structural changes (including of changes to buildings, pipework and engineering);
- [redacted]% indicated that there would be reliance upon external disposal contractors; and
- [redacted]% also stated there would be a need to alter work routines.

Overall conclusions

The above analysis can be summarised as follows:

- All responses to the English version of the survey originated from the UK, primarily from English cities and mainly from hospital laboratories;

- Siemens Healthineers and other branded analysers are almost equally owned at a rate of [redacted] (range: 10-200). [redacted]% are located in a single building; where multiple locations of relevance, their average number is [redacted] (range: 1-10). The [redacted] models of inquiry make up approximately [redacted]% of all owned analysers;

- The majority of respondents dispose of their wastewater by connecting directly to the drain, with [redacted]% indicating [redacted]% of their wastewater is disposed in this way. Wastewater collected in a sump and manually emptied down the drain was used by [redacted]% of the respondents. [redacted]% of responses indicated [redacted] (range: 1,000-10,000) wastewater per annum is generated by their analysers. Respondents typically did not have access to a central waste system and primarily use WWTP there is such an approach; and

- Participants expressed concerns about the costs associated with changing their current wastewater management processes. The majority indicated the need for structural changes and increased costs; however, quantified estimates were not provided.

10 Appendix 2: Proportionality of Additional Risk Management Measures

10.1 Summary

It is important to note before discussing the challenges of additional Risk Management Measures for end-users of OPE-containing IVD products that OPE concentrations in wastewater from diagnostic analyser systems are generally very low and therefore the volume of wastewater will typically be very high in proportion to the mass fraction of OPE. Estimated calculations of these proportions are presented below.

It is also important to consider the current legal framework in the EEA for managing wastewater from diagnostic analysers, which also currently is still applied in the UK (reflected in the NHS Guidance document (HTM 07-01) "Management and disposal of healthcare waste"[11], whereby the low concentration in the effluent leads to an acceptance as wastewater that may be released to the public sewer system, as it is treated as "domestic" wastewater and are usually part of the healthcare institution permits. As a consequence of that, the liquid effluent from the analyser is not considered waste in the meaning of the EU's Waste Framework Directive and the European waste list. On this basis, it will usually not be classified as waste and undergo waste classification on the basis of the UK requirements. Furthermore, on the basis of the current criteria for the classification of hazardous waste, the low OPE concentrations would not trigger a classification of a waste as hazardous, and therefore there would be no legal requirement to incinerate that waste fraction. This is discussed in further detail in the following text.

Based on these, the following conclusions can be drawn with regard to a changed approach to wastewater treatment resulting from the use of diagnostic products in the UK:

1. The current practice of discharging diagnostic analyser wastewater to the public sewer system is in line with the UK and EU regulatory framework for wastewater and waste management.

2. To segregate and ensure incineration of wastewater, customers would need to classify the wastewater not only as waste but specifically as 'hazardous waste' to ensure proper treatment that prevents emissions during waste treatment[12] despite the fact it does not meet the criteria for classification as hazardous waste under the Waste Framework Directive and in accordance with UK requirements based on this.

[11] https://www.england.nhs.uk/publication/management-and-disposal-of-healthcare-waste-htm-07-01/

[12] More specifically: prevents the treatment of waste in wastewater treatment plants or chemical biological treatment plants (CBP) which are still capable of removing OPE specifically or which lead to residues/sludges from these plants being returned to arable land.

3. Volumes of wastewater generated are very high in relation to the volume of OPEs used by customers, thus high incineration cost result from the incineration of the wastewater compared to the amount of OPE removed.

4. There are environmental impacts associated with incinerating high volumes of dilute wastewater which are described and estimated below.

5. There are some significant logistical challenges in separately collecting wastewater, particularly in certain cases, e.g. large laboratory in an old building.

6. The costs of segregating the high volume of wastewater would be significant for healthcare providers, and bearing in mind that many customers are publicly-funded or 'not for profit' organisations.

Based on these aspects, it is considered that a move to segregation of wastewater for all customers would produce significant financial and logistical issues for a significant proportion of healthcare institutions in the EEA, with minimisation of emissions via phase out of OPEs in IVD products a far more viable and effective route.

10.2 Rationale

10.2.1Disposal of residual liquid fractions from the use of IVD products

IVD products, such as the diagnostic reagents and wash solutions in the scope of this AfA, are used on several different analyser systems as described earlier in the main part of this AoA-SEA document. After the measurement procedure which provides a diagnostic patient result is performed, a liquid fraction composed of all the different kit reagents, purified water and the applied wash solutions is generated and then discharged as wastewater in one of two ways:

- The analyser system is directly connected to the sewer system with no human interaction with the waste-water in terms of ensuring drainage via a permitted discharge point; or

- The analyser system collects waste-water in a sump beneath the analyser, which, when full, must be transferred manually to a drainage point within the laboratory/building.

In both cases the liquid fractions are often released to the public sewer system and thereby end up in urban wastewater treatment facilities. It should be noted that subsequent discussions are founded on these fractions, which have higher concentrations of OPE than the actual effluent of wastewater treatment plants as presented in the CSR. Only in exceptional cases when a large fraction of the liquid is not water, is the liquid effluent separately collected and disposed of as waste.

10.2.2 Collection of OPE fractions from IVD activities

Customer profiles

The analyser platforms are located in a variety of different customer sites that may vary with regard to their size and set up. Customer site sizes generally fall within the following scenarios:

- **Small doctor´s surgery**: one or two analysers (only use #1 systems). Limited throughput, analysers in one room of the building ⇒ wastewater fraction < 100 L/week, one or two discharge points, analyser effluent is either directly connected to sewer or to a collection container that is emptied to a sewer manually;

- **Small to mid-size hospital** (usually use #1 systems, only one use #2 system max.): several analysers, may be located in different departments of the hospital ⇒ wastewater fraction < 1000L/week per location, could be several discharge points, analyser effluent is either directly connected to sewer or to a collection container that is emptied to a sewer manually;

- **Large contract laboratory** (use#1 and #2 systems in place): several analysers are located in one or more dedicated buildings ⇒ wastewater fraction < 5000L/week per location, could be several discharge points, analyser effluent is either directly connected to sewer or to a collection container that is emptied to a sewer manually; and

- **Large hospital** (use#1 and #2 systems in place): several analysers are located in different departments of the hospital, additionally there may be one large central laboratory that processes internal and external patient samples ⇒ wastewater fraction < 100L/week per location in hospital + up to 5000 L/week from central laboratory.

In the following text we address in brief –

- **Anticipated Volumes of Wastewater**
- **Costs of Collecting Wastewater – Incineration and Installing Drainage**
- **Practical Considerations of Installing New Drainage**
- **Environmental Impacts of Collecting Wastewater**
- **Interface with waste legislation**

Anticipated Volumes of Wastewater

As previously stated, the concentrations of OPE in wastewater from diagnostic analysers are generally very low and therefore the volume of wastewater to incinerate will, proportionally, be very high. In terms of uses in scope of this AfA, an indication of the volumes generated is provided below.

Table 3: Volumes and costs of collecting wastewater per Applied for Use in 2021, then in 2026

#A

#A

As noted above the tonnage of OPE released from one analyser system annually in the EU is extremely low, while the volume of wastewater can be extremely high in comparison.

This very low volume of OPE diluted in a large quantity of wastewater is then treated at the WwTP. While it is clear that a significant portion of this OPE will be removed as part of this treatment process, in particular at high efficiency treatment plants (see EC Waste-Water Treatment Map), it is unfortunately **impossible to measure the efficiency of removal due to the range of treatment technologies in use across the EU** and as it is not possible to establish what other inputs of OPE there are from other sources entering these facilities. For this reason we have **had to assume the very worst case for the CSR calculations,** though this **will not reflect reality and releases will be significantly lower due to the treatment processes.**

Costs of Collecting Wastewater - Incineration

Table 1 shows **the estimated annual costs of incinerating the waste-water** generated by our systems. This does not include transport costs or costs of retrofitting drainage systems, which are discussed afterwards. It also does not take any account of the environmental externalities, including indirect health effects, associated with transport (e.g. CO_2 emissions) and increased incineration. Even so, the disproportionate nature of these costs is clear.

It is understood that the SEAC uses the results of the study carried out by IVM in 2015 to provide benchmarks for assessing the cost-effectiveness of measures to substitute or reduce emissions of PBT/vPvB substances to the environment. According to this study measures with costs above €50,000 per kg PBT substituted are indicated as likely to be disproportionate from a cost-effectiveness perspective. **Just the incineration of analyser wastewater** (not to mention inevitably arising other costs e.g. drain re-routing) **will lead to costs much higher of £185K per year per kilogram of 4-tert-OP, increasing to £927K per kg saved by 2026**. All such additional costs would fall on the shoulders of the UK healthcare system. From a cost-effectiveness perspective, **these costs are disproportionate** as they are **significantly higher than the upper margin of the "grey" zone defined by IVM (2015**).

Costs of Installing New Drainage Systems

To set up the facilities to collect and store wastewater from analyser systems for subsequent transport to incineration plants which are currently directly plumbed into drainage networks in many institutions is an impractical and extremely costly requirement. A high throughput analyser system can produce up to 960L of dilute wastewater in a day.

Given the significant variability in DU healthcare settings and the types and number of analyser systems used by each DU, it is not possible to quantify exact costs of the work required. However, based on information shared by companies at the MedTech Europe Trade Association level and experience of Facilities Management personnel, we understand **DU's could expect costs between**

€20-100K (per DU) in certain environments. This is of course in addition to the costs per tonne of then transporting and incinerating the collected wastewater.

Practical Considerations of Installing New Drainage Systems

There are **significant impracticalities** in requiring EU healthcare institutions, particularly hospital environments, to **install new collection and drainage systems for large quantities of wastewater**. For larger institutions we expect this would require a new drainage system to transfer the wastewater to the external part of the building.

As per the volumes table above, these changes in infrastructure would only be necessary for 3 years as the volume depletes significantly by end 2025.

- With testing laboratories often located in different parts of the building and on different floors, a new drainage system may require the installation of multiple drainage points, an internal drainage network and presumably also require installation of a wastewater capture system (i.e. tank) external to the building.
- Some hospitals are very old buildings, where re-routing drainage systems can pose serious issues. This can be due to very thick walls, limited space, and drainage networks having to be routed through flooring. Thus, significant disruption could be expected as part of the civils work required.
- Routing drainage may not be possible in some settings, as networks would need to route through wards, clean rooms etc., this being a particular problem in older buildings and those in inner city settings where space is at a premium.
- In cases where a gravity-fed system was not possible (e.g. laboratory on ground floor and only available external location for wastewater capture was at the same or higher level) a pump system would need to be installed, requiring the installation of a power supply and associated electrical circuitry;
- The external collection point must be located where a tanker (or flat-bed lorry if collecting removable IBC's) could safely manoeuvre to access the collection system to remove the wastewater.
- The external system would also require the installation of bunding to ensure secondary containment of the waste liquid and protection of the local environment (also normally a legal requirement)
- Manual handling for healthcare operatives is another consideration. In laboratories where wastewater is currently directly discharged to the public sewer system, operators would need to start collecting wastewater in sumps and transferring the wastewater to a separate drainage point (except in cases where it was possible to route a new network from each individual analyser)

As such, the installation of drainage networks and collection facilities and then transporting to incineration facilities will not be possible in a number of cases, and therefore not technically or practically possible to implement the conditions.

Accessing Incinerators

The access to suitable incineration plants varies across the EU, and in the UK. Distances to suitable hazardous waste incineration plants can vary from about 100 up to 1,500 km. As such, it may not be

possible for customers in certain regions to readily access these plants without long distance transport.

Environmental Impacts

Incineration of the required thousands of tonnes of wastewater per annum has the following environmental consequences, please see **Table 2** for calculations for the UK (Area 2):

- **Transporting** this vast quantity of wastewater by road will result in **significant consumption of fuel** (and in consequence CO_2 emissions). We calculate[13] -
  - By lorry, 40 t: 5 – 53 kg CO2 per ton liquid waste
  - By truck, 3.5t-7.5 t: 14-146 kg CO2 per ton liquid waste (in case of no access to incinerators in an area this could be 150 – 192 kg CO2 per ton liquid waste)
- The **incineration itself also causes emissions of CO_2** (between 810 – 880 kg/t (reference treatment in municipal wastewater treatment 0,3 kg/t))
- It must also be taken into account the generation of **additional traffic**, and which also results in impacts such as **noise generation** and increased accident risks.

[13] For references see Table 4

Table 4: Transport key information and environmental impact based on diesel consumption/CO_2 generation[14] (reference no transport – sewer disposal) and CO_2 generation during incineration[15] (reference household waste water treatment (0.3 kg CO_2 per ton waste water[16])

Area	Area surface [km²][17]	Average distance to incineration plant in area [km]		CO2-Emission, lorry, 40t, per tonne [kg]		CO2-Emissions, lorry, 7,5-12tper tonne [kg]		CO2-Emissions, truck, 3.5t-7.5t per tonne [kg]		CO2-Emissions per tonne incinerated [kg]
		WI[18]	HWI[19][3]	WI	HWI	WI	HWI	WI	HWI	
Area 1: Southwest (ES,PT)	598.170	429	223	20	10	40	21	56	29	810-880
Area 2: Northwest (IR, UK)	318.333	1.128	107	53	5	106	10	146	14	
Area 3: Central West (BE, DE, DK, FR, LI, LU, MT, NE, IT)	1.369.149	131	109	6	5	12	10	17	14	
Area 4: North (FI, NO, SE)	1.100.773	276	525	13	25	26	49	36	68	
Area 5: Baltic	175.086	N.A.[20]	N.A	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	
Area 6: Central East (AT, CZ, HU, PL, SI, SK)	637.745	376	399	18	19	35	37	49	52	
Area 7: South East (BG, CY, GR, RO)	490.061	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	
Transport from Area 5: Baltic to Area 4: North[21]	-	808	1.160	38	54	76	109	105	150	
Transport Area 5: Baltic to Area 6: Central East	-	951	1.217	45	57	89	114	123	158	
Transport Area 7: South East to Area 6: Central East	-	1.232	1.499	58	70	115	140	160	194	

[14] Basis LCA data from GEMIS - Global Emissions Model for integrated Systems http://iinas.org/gemis.html

[15] Basis LCA data from Protocol for the quantification of greenhouse gases emissions from waste management activities – Version 5 – October 2013 http://www.epe-asso.org/en/protocol-quantification-greenhouse-gases-emissions-waste-management-activities-version-5-october-2013/

[16] Basis LCA data from GEMIS - Global Emissions Model for integrated Systems http://iinas.org/gemis.html

[17] Basis Eurostat Area by NUTS 3 region[demo_r_d3area] (reference year 2015) http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do

[18] Waste Incinerators: These Incinerators are dedicated for regular household waste, but it can be the case that they have permissions to incinerate some hazardous wastes. Therefore they are included here as best case. Since it is assume that most of the sites existing cannot handle hazardous liquid waste it has been assumed that only 1/8 (12.5%) of the sites can accept that waste type.

[19] Hazardous waste incinerators: These Waste incinerators differ from their potential to incinerate liquid wastes. Furthermore, incinerators are covered that belong to individual companies or industry parks and do not accept waste from external third parties. For simplicity it was assumed all installations do accept the OPE containing waste

[20] non applicable, reason no sites were identified/have been reported in BREF

[21] Average maximum distance to neighbour area + average distance to installation in the receiving area.

Interface with Waste Legislation

The analysis of the general legal situation for liquid fractions from diagnostic operations has indicated that in most countries it is accepted practice that wastewater is diverted to urban wastewater treatment plants, and that this is in accordance with existing EU and national UK legislation based on national permits or other considerations. Therefore, it is very likely that a transition of the disposal practice towards waste collection and disposal would result in major organisational and economic burden. The latter would be even more significant as only a classification as hazardous waste would in most cases (see exception in previous section) ensure relevant destruction and avoid emissions to the environment with a high degree of certainty.

A change of current practice would also mean that the existing rules for treating such liquid fractions would be overwritten by the Authorisation conditions twice. Firstly, end-users would be in a position where they could not accept the assessment of their wastewater by regional wastewater authorities as acceptable for the public sewer system they govern. Secondly, the rules for classification of waste under the Waste Framework Directive and national UK waste legislation would not be applied correctly, i.e. a more stringent measure would be applied under the Authorisation conditions to treat the waste differently to the way the legislator and the authorities might have foreseen in such cases [22].

Summary/Conclusion

In summary, collection of wastewater **cannot be fulfilled by most customers as it is technically and practically infeasible and due to the significant disproportionate costs and impracticalities for UK healthcare institutions such as hospitals, clinics and laboratories.**

Siemens Healthineers is **already making enormous efforts to eliminate OPE emissions** related to these uses by reformulating or phasing out a vast number of products with the **aim of minimising disruptions to healthcare systems**. Wastewater collection would ultimately **achieve the same objective** as reformulation but **increase exponentially the economic burden for healthcare institutions**.

The OPE Substitution Plan will see releases minimised and significantly decrease by end 2025 by >90% across all downstream users in the UK, achieving the same objective as these proposed conditions in a practical and achievable way with minimal disruption to healthcare systems.

[22] Due to the limit values laid down in Annex III of the Waste Framework Directive for deciding on mirror entries, which are all not exceeded without exception when waste water is assessed with regard to OPE.